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(54) Title: PRODRUGS OS ASPARTYL PROTEASE INHIBITORS

(57) Abstract

The present invention relates to prodrugs of a class of sulfonamides which are aspartyl protease inhibitors. In one embodiment, this invention relates to a novel class of prodrugs of HIV aspartyl protease inhibitors characterized by favorable aqueous solubility, high oral bioavailability and facile *in vivo* generation of the active ingredient. This invention also relates to pharmaceutical compositions comprising these prodrugs. The prodrugs and pharmaceutical compositions of this invention are particularly well suited for decreasing the pill burden and increasing patient compliance. This invention also relates to methods of treating mammals whith these prodrugs and pharmaceutical compositons.

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PRODRUGS OF ASPARTYL PROTEASE INHIBITORS

TECHNICAL FIELD OF THE INVENTION

The present invention relates to prodrugs of a class of sulfonamides which are aspartyl protease inhibitors. In one embodiment, this invention relates to a novel class of prodrugs of HIV aspartyl protease inhibitors characterized by favorable aqueous solubility, high oral bioavailability and facile *in vivo* generation of the active ingredient. This invention also relates to pharmaceutical compositions comprising these prodrugs. The prodrugs and pharmaceutical compositions of this invention are particularly well suited for decreasing the pill burden and increasing patient compliance. This invention also relates to methods of treating mammals with these prodrugs and pharmaceutical compositions.

BACKGROUND OF THE INVENTION

Aspartyl protease inhibitors are considered the most effective current drug in the fight against HIV infection. These inhibitors, however, require certain physicochemical properties in order to achieve good potency against the enzyme. One of these properties is high hydrophobicity. Unfortunately, this property results in poor aqueous solubility and low oral bioavailability.

United States Patent 5,585,397 and WO 95/24385 describes a class of sulfonamide compounds

that are inhibitors of the aspartyl protease enzyme. These compounds illustrate the drawbacks concomitant to pharmaceutical compositions comprising hydrophobic aspartyl protease inhibitors. For example, VX-478 (4-amino-N-((2-syn,3S)-2-hydroxy-4-phenyl-2((S)-tetrahydrofuran-3-yl-oxycarbonylamino)-butyl-N-isobutyl-benzenesulfonamide) is an aspartyl protease inhibitor disclosed in the '397 patent. It has a relatively low aqueous solubility. While the oral bioavailability of this inhibitor in a "solution" formulation is excellent, the dosage of VX-478 in this form is severely limited by the amount of liquid present in the particular liquid dosage from, e.g., encapsulated into a soft gelatin capsule. A higher aqueous solubility would increase drug load per unit dosage of VX-478.

Currently, the solution formulation of VX-478 produces an upper limit of 150 mg of VX-478 in each capsule. Given a therapeutic dose of 2400 mg/day of VX-478, this formulation would require a patient to consume 16 capsules per day. Such a high pill burden would likely result in poor patient compliance, thus producing sub-optimal therapeutic benefit of the drug. The high pill burden is also a deterrent to increasing the amount of the drug administered per day to a patient. Another drawback of the pill burden and the concomitant patient compliance problem is in the treatment of children infected with HIV.

Furthermore, these "solution" formulations, such as the mesylate formulation, are at a saturation solubility of VX-478. This creates the real potential of having the drug crystallize out of solution under various storage and/or shipping conditions. This, in turn, would likely result in a loss of some of the oral bioavailability achieved with VX-478.

One way of overcoming these problems associated with aspartyl protease inhibitors is to develop a standard solid dosage form, such as a tablet or a capsule or a suspension form. Unfortunately, such solid dosage forms have much lower oral bioavailability of the drug.

Thus, there is a need to improve the drug load per unit dosage form for aspartyl protease inhibitors. Such an improved dosage form would reduce the pill burden and increase patient compliance. It would also provide for the possibility of increasing the amounts of the drug administered per day to a patient.

SUMMARY OF THE INVENTION

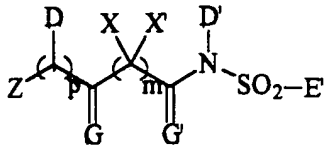
The present invention provides novel prodrugs of a class of sulfonamide compounds that are inhibitors of aspartyl protease, in particular, HIV aspartyl protease. These prodrugs are characterized by excellent aqueous solubility, increased bioavailability and are readily metabolized into the active inhibitors *in vivo*. The present invention also provides pharmaceutical compositions comprising these prodrugs and methods of treating HIV infection in mammals using these prodrugs and the pharmaceutical compositions thereof.

These prodrugs can be used alone or in combination with other therapeutic or prophylactic agents, such as anti-virals, antibiotics, immunomodulators or vaccines, for the treatment or prophylaxis of viral infection.

It is a principal object of this invention to provide a novel class of prodrugs of sulfonamide compounds that are aspartyl protease inhibitors, and

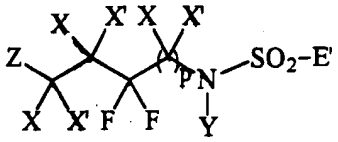
particularly, HIV aspartyl protease inhibitors. This novel class of sulfonamides is represented by formulas I and II:

Formula I:



(I)

Formula II:



(II)

wherein:

each Z is selected from the group consisting of $-N(D)SO_2E$; $-N(H)A$; $-N(D)A$; $-N(H)E$; $-N(H)C(O)N(D)(E)$; $-N(H)-Ht$; $-Ht$ and $-N(D)-Ht$;

each A is independently selected from the group consisting of H; Ht; $-R^1-Ht$; $-R^1-C_1-C_6$ alkyl, which may be optionally substituted with one or more groups selected from the group consisting of hydroxy, C_1-C_4 alkoxy, Ht, -O-Ht, $-NR^2-CO-N(R^2)(R^2)$, $-NR^2-CO-OR^2$ and $-CO-N(R^2)(R^2)$; and $-R^1-C_2-C_6$ alkenyl, which may be optionally substituted with one or more groups selected from the group consisting of hydroxy, C_1-C_4 alkoxy, Ht, -O-Ht, $-NR^2-CO-N(R^2)(R^2)$, $-CO-N(R^2)(R^2)$ or R^{10};

each Ht is independently selected from the group consisting of C_3-C_7 cycloalkyl; C_5-C_7 cycloalkenyl; C_6-C_{10} aryl; phenyl fused with heterocycle; and heterocycle; wherein any member of said Ht may be optionally substituted with one or more substituents selected from the group consisting of oxo, $-OR^2$, $-R^2$, $-N(R^2)(R^2)$, -NHOH, $-R^2$-OH, -CN, $-CO_2R^2$, $-C(O)-N(R^2)(R^2)$, $-S(O)_2-N(R^2)(R^2)$, $-N(R^2)-C(O)-R^2$, $-C(O)-R^2$, $-S(O)_n-R^2$, $-OCF_3$, $-S(O)_n-D$, $-N(R^2)-S(O)_2(R^2)$, halo, $-CF_3$, $-NO_2$, $-R^6$, $-O-R^6$, $-C(O)N(D)(D)$ and $-C(O)N(H)D$, $-OR^{10}$, $-SR^{10}$, $-R^{10}$, $-N(R^2)(R^{10})$ or $-N(R^{10})_2$;

each D and D' is independently selected from the group consisting of R^6; $-N(R^2)(R^2)$; C_1-C_6 alkyl, which may be optionally substituted with one or more groups selected from C_3-C_6 cycloalkyl, $-OR^2$, $-R^3$, $-O-R^6$ $-S-R^6$ and R^6; C_2-C_4 alkenyl, which may be optionally substituted with one or more groups selected from the group consisting of C_3-C_6 cycloalkyl, $-OR^2$, $-R^3$, $-O-R^6$ and R^6; C_3-C_6 cycloalkyl, which may be optionally substituted with or fused with R^6; and C_5-C_6 cycloalkenyl, which may be optionally substituted with or fused with R^6;

each E and E' is independently selected from the group consisting of Ht; -O-Ht; Ht-Ht; $-O-R^3$; $-NR^2R^3$; C_1-C_6 alkyl, which may be optionally substituted with one or more groups selected from the group consisting of R^{10}, R^4 and Ht; and C_2-C_6 alkenyl, which may be optionally substituted with one or more groups selected from the group consisting of R^{10}, R^4 and Ht;

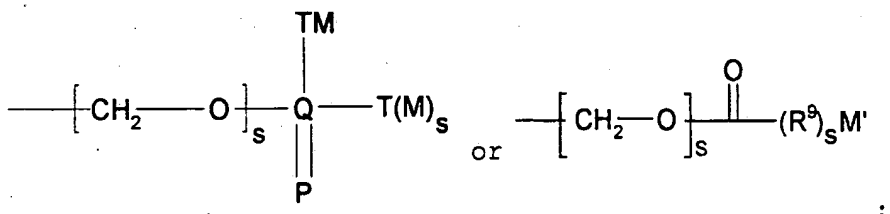
each R^1 is independently selected from the group consisting of $-C(O)-$, $-S(O)_2-$, $-C(O)-C(O)-$, $-O-C(O)-$, $-O-S(O)_2$, $-NR^2-S(O)_2-$, $-NR^2-C(O)-$ and $-NR^2-C(O)-C(O)-$;

each R^2 is independently selected from the group consisting of H, $-R^6$, and C_1-C_4 alkyl optionally substituted with R^6;

each R^3 is independently selected from the group consisting of H, Ht, C_1-C_6 alkyl and C_2-C_6 alkenyl wherein any member of said R^3, except H, may be optionally substituted with one or more substituents selected from the group consisting of $-OR^2$, $-C(O)-NH-R^2$, $-S(O)_n-N(R^2)(R^2)$, Ht, $-CN$, $-SR^2$, $-CO_2R^2$, $NR^2-C(O)-R^2$;

each R^4 is independently selected from the group consisting of $-OR^2$, $-C(O)-NHR^2$, $-S(O)_2-NHR^2$, halo, $-NR^2-C(O)-R^2$, $-CN$, $-N(R^2)(R^2)$, $-NO_2$, $-C(O)N(D)(D)$ and $-C(O)N(H)D$;

each R^{10} is independently selected from



;

wherein each M is independently selected from H, Li, Na, K, Mg, Ca, Ba, $-N(R^2)_4$, C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl, or $-R^6$; wherein 1 to 4 $-CH_2$ radicals of the alkyl or alkenyl group, other than the $-CH_2$ that is bound to T, is optionally replaced by a heteroatom group selected from O, S, S(O), $S(O_2)$, or $N(R^2)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, $-OR^2$, $-R^2$, $N(R^2)_2$, $N(R^2)_3$, R^2OH, $-CN$, $-CO_2R^2$, $-C(O)-N(R^2)_2$, $S(O)_2-N(R^2)_2$, $N(R^2)-C(O)-R_2$, $C(O)R^2$, $-S(O)_n-R^2$, OCF_3, $-S(O)_n-R^6$, $N(R^2)-S(O)_2(R^2)$, halo, $-CF_3$, or $-NO_2$;

M' is H, C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl, or $-R^6$; wherein 1 to 4 $-CH_2$ radicals of the alkyl or alkenyl

group is optionally replaced by a heteroatom group selected from O, S, S(O), $S(O_2)$, or $N(R^2)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, $-OR^2$, $-R^2$, $-N(R^2)_2$, $N(R^2)_3$, $-R^2OH$, -CN, $-CO_2R^2$, $-C(O)-N(R^2)_2$, $-S(O)_2-N(R^2)_2$, $-N(R^2)-C(O)-R_2$, $-C(O)R^2$, $-S(O)_n-R^2$, $-OCF_3$, $-S(O)_n-R^6$, $-N(R^2)-S(O)_2(R^2)$, halo, $-CF_3$, or $-NO_2$;

T is O, S, $N(R^2)_2$, or, when M is absent, H;

Q is P or S;

P is O or S; and

each s is independently 0 or 1;

R^9 is $C(R^2)_2$, O or $N(R^2)$; and wherein when Q is S, T is not S; and

each R^6 is independently selected from the group consisting of aryl, carbocycle and heterocycle, wherein said carbocycle or heterocycle may be optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^5$, $-R^5$, $-N(R^5)(R^5)$, $-N(R^5)-C(O)-R^5$, $-R^5-OH$, -CN, $-CO_2R^5$, $-C(O)-N(R^5)(R^5)$, halo and $-CF_3$;

each R^5 is independently selected from the group consisting of H and C_1-C_3 alkyl;

each n is independently 1 or 2;

m is an integer selected from 1, 2 and 3;

p is an integer selected from 0 and 1;

each G and G' is independently selected from the group consisting of H_2 and O;

each X and X' is independently selected from the group consisting of hydrogen; -OH; $-NH_2$; -SH; D; $-OR^{10}$, halogen and, if X and X' are taken together, oxygen;

provided that at least one X or X' is $-OR^{10}$ and the other geminal X' or X is H; and

each Y is independently selected from the group consisting of hydrogen and D.

It is also an object of this invention to provide pharmaceutical compositions comprising the sulfonamides of formulas I and II, methods for preparing those sulfonamides, and methods for their use as inhibitors of aspartyl protease, and particularly, HIV aspartyl protease,

It is a further object of this invention to provide methods for treating viral diseases, and in particular HIV-related diseases, using the compounds and compositions of this invention.

DETAILED DESCRIPTION OF THE INVENTION

In order that the invention herein described may be more fully understood, the following detailed description is set forth. In the description, the following abbreviations are used:

Designation	Reagent or Fragment
Ac	acetyl
Me	methyl
Et	ethyl
Bn	benzyl
Trityl	triphenylmethyl
Asn	D- or L-asparagine
Ile	D- or L-isoleucine
Phe	D- or L-phenylalanine
Val	D- or L-valine
Boc	tert-butoxycarbonyl
Cbz	benzyloxycarbonyl (carbobenzyloxy)
Fmoc	9-fluorenylmethoxycarbonyl
DCC	dicyclohexylcarbodiimide
DIC	diisopropylcarbodiimide

EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HOBt	1-hydroxybenzotriazole
HOSu	1-hydroxysuccinimide
TFA	trifluoroacetic acid
DIEA	diisopropylethylamine
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
EtOAc	ethyl acetate
t-Bu	tert-butyl
iBu	iso-butyl
DMF	dimethylformamide
THP	tertrahydropyran
THF	tetrahydrofuran
DMSO	dimethylsulfoxide

The following terms are employed herein:

Unless expressly stated to the contrary, the terms "$-SO_2-$" and "$-S(O)_2-$" as used herein refer to a sulfone or sulfone derivative (i.e., both appended groups linked to the S), and not a sulfinate ester.

The term "alkyl", alone or in combination with any other term, refers to a straight-chain or branched-chain saturated aliphatic hydrocarbon radical containing the specified number of carbon atoms, or where no number is specified, preferably from 1-10 and more preferably from 1-5 carbon atoms. Examples of alkyl radicals include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, n-hexyl and the like.

The term "alkoxy" refers to an alkyl ether radical, wherein the term "alkyl" is as defined above. Examples of suitable alkyl ether radicals include, but are not limited to, methoxy, ethoxy, n-propoxy,

isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy and the like.

The term "alkenyl", alone or in combination with any other term, refers to a straight-chain or branched-chain mono- or poly-unsaturated aliphatic hydrocarbon radical containing the specified number of carbon atoms, or where no number is specified, preferably from 2-10 carbon atoms and more preferably, from 2-6 carbon atoms. Examples of alkenyl radicals include, but are not limited to, ethenyl, E- and Z-propenyl, isopropenyl, E- and Z-butenyl, E- and Z-isobutenyl, E- and Z-pentenyl, E- and Z-hexenyl, E,E-, E,Z-, Z,E- and Z,Z-hexadienyl and the like.

The term "anti-viral agent" or "anti-retroviral agent" refers to a compound or drug which possesses viral inhibitory activity. Such agents include reverse transcriptase inhibitors (including nucleoside and non-nucleoside analogs) and protease inhibitors. Preferably the protease inhibitor is an HIV protease inhibitor. Examples of nucleoside analog reverse transcriptase inhibitors include, but are not limited to, zidovudine (AZT), dideoxycytidine (ddC), didanosine (ddI), stavudine (d4T), 3TC, 935U83, 1592U89 and 524W91. Examples of non-nucleoside analog reverse transcriptase inhibitors include, but are not limited to TIBO, delavirdine (U90) and nevirapine. Examples of HIV protease inhibitors include, but are not limited to, saquinavir (Ro 31-8959), L-735,524, ABT 538 (A80538), AG 1341, XM 412, XM 450, BMS 186318 and CPG 53,437.

The term "aryl", alone or in combination with any other term, refers to a carbocyclic aromatic radical (such as phenyl or naphthyl) containing the specified number of carbon atoms, preferably from 6-14 carbon atoms, and more preferably from 6-10 carbon

atoms. Examples of aryl radicals include, but are not limited to phenyl, naphthyl, indenyl, indanyl, azulenyl, fluorenyl, anthracenyl and the like.

The term "backbone" refers to the structural representation of a compound of this invention, as set forth in the figures drawn in this application.

The term "carbocycle" refers to a non-aromatic stable 3- to 8-membered carbon ring which may be saturated, mono-unsaturated or poly-unsaturated. The carbocycle may be attached at any endocyclic carbon atom which results in a stable structure. Preferred carbocycles have 5-6 carbons.

The term "heterocycle", unless otherwise defined herein, refers to a stable 3-7 membered monocyclic heterocyclic ring or 8-11 membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which may be optionally benzofused if monocyclic. Each heterocycle consists of one or more carbon atoms and from one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. As used herein, the terms "nitrogen and sulfur heteroatoms" include any oxidized form of nitrogen and sulfur, and the quaternized form of any basic nitrogen. In addition, any ring nitrogen or carbon may be optionally substituted with a substituent R^2, as defined herein for compounds of formula I or II. A heterocycle may be attached at any endocyclic carbon or heteroatom which results in the creation of a stable structure. Preferred heterocycles include 5-7 membered monocyclic heterocycles and 8-10 membered bicyclic heterocycles. Preferred heterocycles defined above include, for example, benzimidazolyl, imidazolyl, imidazolinoyl, imidazolidinyl, quinolyl, isoquinolyl, indolyl, indazolyl, indazolinolyl, perhydropyridazyl, pyridazyl, pyridyl, pyrrolyl, pyrrolinyl, pyrrolidinyl,

pyrazolyl, pyrazinyl, quinoxolyl, piperidinyl, pyranyl, pyrazolinyl, piperazinyl, pyrimidinyl, pyridazinyl, morpholinyl, thiamorpholinyl, furyl, thienyl, triazolyl, thiazolyl, ß-carbolinyl, tetrazolyl, thiazolidinyl, benzofuranoyl, thiamorpholinyl sulfone, oxazolyl, benzoxazolyl, oxopiperidinyl, oxopyrroldinyl, oxoazepinyl, azepinyl, isoxazolyl, isothiazolyl, furazanyl, tetrahydropyranyl, tetrahydrofuranyl, thiazolyl, thiadiazoyl, dioxolyl, dioxinyl, oxathiolyl, benzodioxolyl, dithiolyl, thiophenyl, tetrahydrothiophenyl, sulfolanyl, dioxanyl, dioxolanyl, tetrahydrofurodihydrofuranyl, tetrahydropyranodihydrofuranyl, dihydropyranyl, tetrahydrofurofuranyl and tetrahydropyranofuranyl.

The term "halo" refers to a radical of fluorine, chlorine, bromine or iodine.

The terms "HIV protease" and "HIV aspartyl protease" are used interchangeably and refer to the aspartyl protease encoded by the human immunodeficiency virus type 1 or 2. In a preferred embodiment of this invention, these terms refer to the human immunodeficiency virus type 1 aspartyl protease.

The term "substituted", whether preceded by the term "optionally" or not, and substitutions contained in formulas of this invention, refer to the replacement of one or more hydrogen radicals in a given structure with the radical of a specified substituent. When more than one position in a given structure may be substituted with more than one substituent selected from a specified group, the substituents may be either the same or different at every position (for example, the moiety $-N(R^2)(R^2)$ or -phenyl-R^7). Typically, when a structure may be optionally substituted, 0-3 substitutions are preferred, and 0-1 substitutions is more preferred. Most preferred substituents are those

which enhance protease inhibitory activity or intracellular antiviral activity in permissive mammalian cells or immortalized mammalian cell lines, or which enhance deliverability by enhancing solubility characteristics or enhancing pharmacokinetic or pharmacodynamic profiles as compared to the unsubstituted compound. Other more preferred substituents include those used in the compounds shown in Tables 1-8 and the most preferred substituents include those used in the compounds in Tables 1, 5, 6, and 7.

The term "R^2" when used as a linker between two radicals excludes R^2 as H.

The term "-phenyl-R^7" as used herein refers to a phenyl radical having R^7, the same or different, at each free position and expressly envisions polycyclic ring systems formed by joining multiple R^7 substituents on the phenyl ring. Preferably, 0-3 R^7 in a particular phenyl radical are not H. In addition to H, -OH, $-OCH_3$, $-NH_2$, $-NO_2$ and CN are preferred R^7. Such ring systems are preferably mono- or bi-cyclic. These ring systems may be carbocyclic or may optionally contain one or more heteroatoms, such as N, O or S. Preferred ring systems include benzimidazolyl, benzoxazolyl, benzothiazolyl, benztriazolyl, imidazolyl, indolyl, isoxazolyl, isothiazolyl, oxazolyl, thianaphthenyl, thiazolyl, and triazolyl.

The term "pharmaceutically effective amount" refers to an amount effective in treating HIV infection in a patient either as monotherapy or in combination with other agents. The term "treating" as used herein refers to the alleviation of symptoms of a particular disorder in a patient or the improvement of an ascertainable measurement associated with a particular disorder. Specifically, with respect to HIV, effective

treatment using the compounds and compositions of this invention would result in an improvement in an HIV associated ascertainable measurement. The term "prophylactically effective amount" refers to an amount effective in preventing HIV infection in a patient. As used herein, the term "patient" refers to a mammal, including a human.

The term "pharmaceutically acceptable carrier or adjuvant" refers to a carrier or adjuvant that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the antiretroviral agent.

As used herein, the compounds of this invention, including the compounds of formula I and II are defined to include pharmaceutically acceptable derivatives thereof. A "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, salt of an ester, or other derivative of a compound of this invention which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention or an inhibitorily active metabolite or residue thereof. Particularly favored derivatives are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a mammal (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or lymphatic system) relative to the parent species.

Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids

and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g., sodium), alkaline earth metal (e.g., magnesium), ammonium and N-(C_{1-4} alkyl)$_4^+$ salts.

The term "thiocarbamates" refers to compounds containing the functional group N-SO_2-O.

The term "if X and X' are taken together, oxygen" refers to a carbonyl formed on the carbon that bears that X and X'. When X and X' are both geminal substituents on the same carbon, if one is -OH the other is H.

The compounds of this invention contain one or more asymmetric carbon atoms and thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be of the R or S configuration. Although the specific compounds exemplified in this application may be depicted in a particular stereochemical configuration, compounds having either the opposite stereochemistry at any given chiral center or mixtures thereof are also envisioned.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., therapeutic or prophylactic administration to a mammal or for use in affinity chromatography applications). Typically, such compounds are stable at a temperature of 40 C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

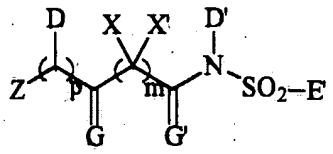
The compounds of the present invention may be used in the form of salts derived from inorganic or organic acids. Included among such acid salts, for example, are the following: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate and undecanoate.

This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. The basic nitrogen can be quaternized with any agents known to those of ordinary skill in the art including, for example, lower alkyl halides, such as methyl, ethyl, propyl and butyl

chloride, bromides and iodides; dialkyl sulfates including dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aralkyl halides including benzyl and phenethyl bromides. Water or oil-soluble or dispersible products may be obtained by such quaternization.

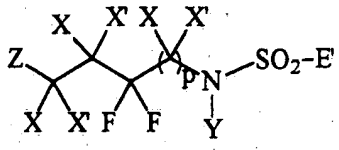
The sulfonamides of this invention are those of formulas I and II:

Formula I:



(I)

Formula II:



(II)

wherein:

each Z is selected from the group consisting of $-N(D)SO_2E$; $-N(H)A$; $-N(D)A$; $-N(H)E$; $-N(H)C(O)N(D)(E)$; $-N(H)-Ht$; $-Ht$ and $-N(D)-Ht$;

each A is independently selected from the group consisting of H; Ht; $-R^1-Ht$; $-R^1-C_1-C_6$ alkyl,

which may be optionally substituted with one or more groups selected from the group consisting of hydroxy, C_1-C_4 alkoxy, Ht, -O-Ht, $-NR^2-CO-N(R^2)(R^2)$, $-NR^2-CO-OR^2$ and $-CO-N(R^2)(R^2)$; and $-R^1-C_2$-C_6 alkenyl, which may be optionally substituted with one or more groups selected from the group consisting of hydroxy, C_1-C_4 alkoxy, Ht, -O-Ht, $-NR^2-CO-N(R^2)(R^2)$, $-CO-N(R^2)(R^2)$ or R^{10};

each Ht is independently selected from the group consisting of C_3-C_7 cycloalkyl; C_5-C_7 cycloalkenyl; C_6-C_{10} aryl; phenyl fused with heterocycle; and heterocycle; wherein any member of said Ht may be optionally substituted with one or more substituents selected from the group consisting of oxo, $-OR^2$, $-R^2$, $-N(R^2)(R^2)$, -NHOH, $-R^2-OH$, -CN, $-CO_2R^2$, $-C(O)-N(R^2)(R^2)$, $-S(O)_2-N(R^2)(R^2)$, $-N(R^2)-C(O)-R^2$, $-C(O)-R^2$, $-S(O)_n-R^2$, $-OCF_3$, $-S(O)_n-D$, $-N(R^2)-S(O)_2(R^2)$, halo, $-CF_3$, $-NO_2$, $-R^6$, $-O-R^6$, $-C(O)N(D)(D)$ and $-C(O)N(H)D$, $-OR^{10}$, $-SR^{10}$, $-R^{10}$, $-N(R^2)(R^{10})$ or $-N(R^{10})_2$;

each D and D' is independently selected from the group consisting of R^6; $-N(R^2)(R^2)$; C_1-C_6 alkyl, which may be optionally substituted with one or more groups selected from C_3-C_6 cycloalkyl, $-OR^2$, $-R^3$, $-O-R^6$ $-S-R^6$ and R^6; C_2-C_4 alkenyl, which may be optionally substituted with one or more groups selected from the group consisting of C_3-C_6 cycloalkyl, $-OR^2$, $-R^3$, $-O-R^6$ and R^6; C_3-C_6 cycloalkyl, which may be optionally substituted with or fused with R^6; and C_5-C_6 cycloalkenyl, which may be optionally substituted with or fused with R^6;

each E and E' is independently selected from the group consisting of Ht; -O-Ht; Ht-Ht; $-O-R^3$; $-NR^2R^3$; C_1-C_6 alkyl, which may be optionally substituted with one or more groups selected from the group consisting of R^{10}, R^4 and Ht; and C_2-C_6 alkenyl, which may be

optionally substituted with one or more groups selected from the group consisting of R^{10}, R^4 and Ht;

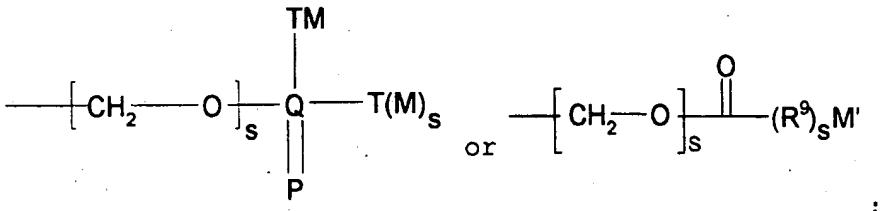
each R^1 is independently selected from the group consisting of $-C(O)-$, $-S(O)_2-$, $-C(O)-C(O)-$, $-O-C(O)-$, $-O-S(O)_2$, $-NR^2-S(O)_2-$, $-NR^2-C(O)-$ and $-NR^2-C(O)-C(O)-$;

each R^2 is independently selected from the group consisting of H, $-R^6$, and C_1-C_4 alkyl optionally substituted with R^6;

each R^3 is independently selected from the group consisting of H, Ht, C_1-C_6 alkyl and C_2-C_6 alkenyl wherein any member of said R^3, except H, may be optionally substituted with one or more substituents selected from the group consisting of $-OR^2$, $-C(O)-NH-R^2$, $-S(O)_n-N(R^2)(R^2)$, Ht, $-CN$, $-SR^2$, $-CO_2R^2$, $NR^2-C(O)-R^2$;

each R^4 is independently selected from the group consisting of $-OR^2$, $-C(O)-NHR^2$, $-S(O)_2-NHR^2$, halo, $-NR^2-C(O)-R^2$, $-CN$, $-N(R^2)(R^2)$, $-NO_2$, $-C(O)N(D)(D)$ and $-C(O)N(H)D$;

each R^{10} is independently selected from



;

wherein each M is independently selected from H, Li, Na, K, Mg, Ca, Ba, $-N(R^2)_4$, C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl, or $-R^6$; wherein 1 to 4 $-CH_2$ radicals of the alkyl or alkenyl group, other than the $-CH_2$ that is bound to T, is optionally replaced by a heteroatom group selected from O, S, S(O), $S(O_2)$, or $N(R^2)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is

optionally replaced with a substituent selected from oxo, $-OR^2$, $-R^2$, $N(R^2)_2$, $N(R^2)_3$, R^2OH, $-CN$, $-CO_2R^2$, $-C(O)-N(R^2)_2$, $S(O)_2-N(R^2)_2$, $N(R^2)-C(O)-R_2$, $C(O)R^2$, $-S(O)_n-R^2$, OCF_3, $-S(O)_n-R^6$, $N(R^2)-S(O)_2(R^2)$, halo, $-CF_3$, or $-NO_2$;

M' is H, C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl, or $-R^6$; wherein 1 to 4 $-CH_2$ radicals of the alkyl or alkenyl group is optionally replaced by a heteroatom group selected from O, S, S(O), $S(O_2)$, or $N(R^2)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, $-OR^2$, $-R^2$, $-N(R^2)_2$, $N(R^2)_3$, $-R^2OH$, $-CN$, $-CO_2R^2$, $-C(O)-N(R^2)_2$, $-S(O)_2-N(R^2)_2$, $-N(R^2)-C(O)-R_2$, $-C(O)R^2$, $-S(O)_n-R^2$, $-OCF_3$, $-S(O)_n-R^6$, $-N(R^2)-S(O)_2(R^2)$, halo, $-CF_3$, or $-NO_2$;

T is O, S, $N(R^2)_2$, or, when M is absent, H;

Q is P or S;

P is O or S; and

each s is independently 0 or 1;

R^9 is $C(R^2)_2$, O or $N(R^2)$; and wherein when Q is S, T is not S; and

each R^6 is independently selected from the group consisting of aryl, carbocycle and heterocycle, wherein said carbocycle or heterocycle may be optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^5$, $-R^5$, $-N(R^5)(R^5)$, $-N(R^5)-C(O)-R^5$, $-R^5-OH$, $-CN$, $-CO_2R^5$, $-C(O)-N(R^5)(R^5)$, halo and $-CF_3$;

each R^5 is independently selected from the group consisting of H and C_1-C_3 alkyl;

each n is independently 1 or 2;

m is an integer selected from 1, 2 and 3;

p is an integer selected from 0 and 1;

each G and G' is independently selected from the group consisting of H_2 and O;

each X and X' is independently selected from the group consisting of hydrogen; $-OH$; $-NH_2$; $-SH$; D;

$-OR^{10}$, halogen and, if X and X' are taken together, oxygen;

provided that at least one X or X' is $-OR^{10}$ and the other geminal X' or X is H; and

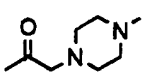
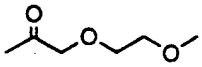
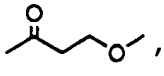
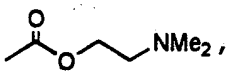
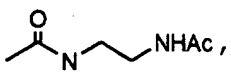
each Y is independently selected from the group consisting of hydrogen and D.

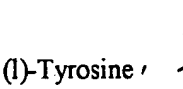
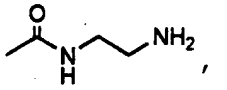
Except where expressly noted to the contrary, the term "[variable] as defined for formula I or II", or any equivalent term used herein, refers to the definitions shown directly above. In addition, where no reference is made to a particular definition for a given variable, the definition is to be taken as that defined for formulas I and II shown directly above.

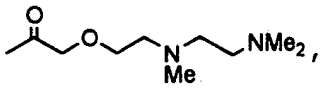
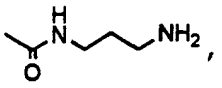
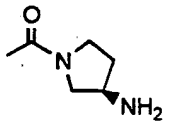
Preferred compounds of formula I include those compounds wherein G or G' or both are oxygen. More preferably, when G or G' or both are oxygen (i.e., form a carbonyl with the carbon to which they are attached), the X and X' on the carbon adjacent to the carbonyl are independently selected from the group consisting of H, OH, F, or taken together, oxygen. Preferably, the compounds of formula I contain from 1 to 4 carbonyls, and more preferably 1 to 3 carbonyls, in the backbone of the structures.

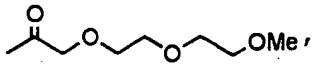
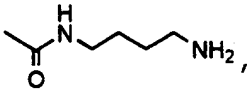
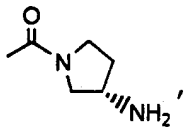
Other preferred compounds of formula I and II are those wherein E' is selected from -Ht and $-R^2$-Ht. More preferred E' are those selected from the group consisting of -phenyl-R^7; carbocycle; heterocycle optionally substituted with -NHAc, alkyl, alkoxy, -OH, $-OR^{10}$ and CF_3; and C_1-C_6 alkyl optionally substituted with Ht wherein Ht may be optionally substituted with -NH-C(O)-C_1-C_3 alkyl, oxo, C_1-C_6 alkyl, alkoxy, -OH, $-OR^{10}$ and CF_3 and wherein R^7 is selected from the group consisting of H, -OH, $-OR^2$, $-R^2$, $-N(R^2)(R^2)$, $-N(R^2)-C(O)-R^2$, $-R^2$, $-OR^{10}$, -OH, -CN, $-CO_2R^2$, $-C(O)-N(R^2)(R^2)$, $-NO_2$, halo and $-CF_3$. Most preferred E' are those selected

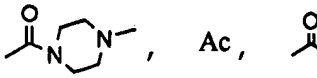
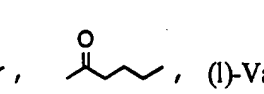
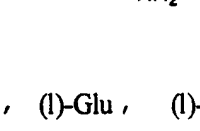
from the group -phenyl-R^7. Preferred R^7 are selected from the group consisting of H, -OH, $-OR^2$, $-R^2$, $-N(R^2)(R^2)$, $-N(R^2)-C(O)-R^2$, and $-NO_2$. Most preferred R^7 are $-NH_2$, -OH and $-OCH_3$. Unless expressly noted to the contrary, the term "R^7" refers to the definitions shown above.

Preferably R^{10} is  ,  ,  , (l)-Lysine, PO_3^{2-},  ,  ,

 ,  , (l)-Serine, SO_3Na_2,

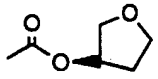
 ,  ,  ,

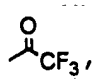
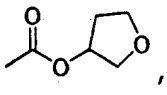
 ,  ,  ,

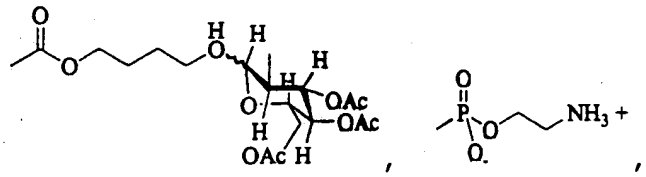
 ,  ,  ,

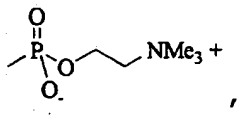
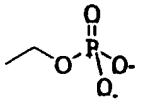
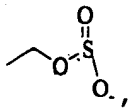
, , ,

, Ac, , , (l)-Val, (l)-Glu, (l)-Asp,

(l)-γ-t-bu-Asp,  , (l)-(l)-3-Pyridyl-alanine, (l)-Histidine,

-CHO, (l)-Valine and  ,  ,

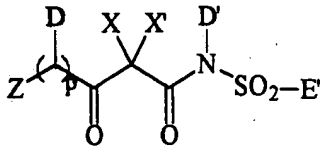


PO_3K_2, PO_3Ca, PO_3-spermine, PO_3-(spermidine)$_2$ or PO_3-(meglamine)$_2$.

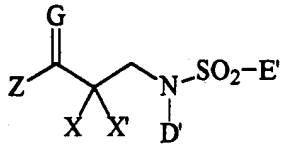
Other preferred compounds of formula I include those compounds having the structures of formulas IV, VI, VII, C and CI:

Formula IV:



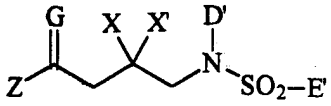
(IV)

Formula VI:



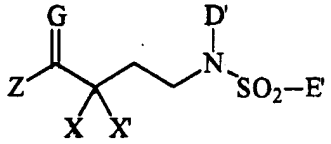
(VI)

Formula VII:



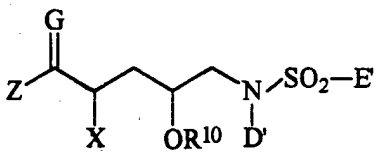
(VII)

Formula C:



(C)

Formula CI:



(CI)

wherein one of X and X' is $-OR^{10}$ and the other of X and X', if present, is H; and the remaining variables are as defined for the compounds of formula I with the exception that in formula C, Z is selected from the group consisting of -N(H)A; -N(D)A; -N(H)E; -N(H)C(O)N(D)(E); -N(H)-Ht; -Ht and -N(D)-Ht. The most preferred compounds of formula I are those compounds of formulas VI, VII, and C.

Preferred compounds of formula IV include those compounds having the following definitions for one or more of the below-specified variables:

each D and D' is independently selected from the group consisting of C_1-C_6 alkyl, which may be optionally substituted with R^6;

each E and E' is independently selected from C_5-C_6 aryl, which may be optionally substituted with R^4;

each R^4 is independently selected from the group consisting of $-OR^2$, $-N(R^2)(R^2)$ and $-NO_2$;

each Z is independently selected from the group consisting of -N(H)Ht; -N(H)A; -N(D)A and -Ht;

each Ht is independently selected from the group consisting of C_6-C_{10} aryl and 5-10 membered saturated or unsaturated heterocycle, wherein any member of said Ht may be optionally substituted with one or more substituents, the same or different, selected from the group consisting of $-OR^2$, R^2, $-N(R^2)(R^2)$, $-NO_2$, $-C(O)N(R^2)(R^2)$ and $-S(O)_n-R^6$, $-OR^{10}$, $-SR^{10}$, $-R^{10}$, $-N(R^2)(R^{10})$ or $-N(R^{10})_2$;

each A is independently selected from the group consisting of H; $-R^1$-Ht and $-R^1$-C_1-C_6 alkyl; and

each R^1 is independently selected from the group consisting of -C(O)- and -O-C(O)-.

Preferred compounds of formula VI include those compounds having the following definitions for one or more of the below-identified variables:

each D and D' is independently selected from the group consisting of C_1-C_6 alkyl, which may be optionally substituted with R^6;

each E' is independently selected from C_5-C_6 aryl, which may be optionally substituted with R^4;

each R^1 is selected from the group consisting of -C(O)- and -O-C(O)-;

each R^4 is independently selected from the group consisting of $-OR^2$, $-N(R^2)(R^2)$ and $-NO_2$;

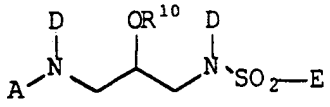
each Z is selected from the group consisting of -N(H)Ht; -N(H)A; -N(D)A and -Ht;

each Ht is independently selected from the group consisting of C_6-C_{10} aryl and 5-10 membered saturated or unsaturated heterocycle, and wherein any member of said Ht may be optionally substituted with one or more substituents, the same or different, selected from the group consisting of $-OR^2$, R^2, $-N(R^2)(R^2)$, $-NO_2$, $-C(O)N(R^2)(R^2)$ and $-S(O)_n-R^6$, $-OR^{10}$, $-SR^{10}$, $-R^{10}$, $-N(R^2)(R^{10})$ or $-N(R^{10})_2$; and

each A is selected from the group consisting of H; $-R^1$-Ht and $-R^1$-C_1-C_6 alkyl.

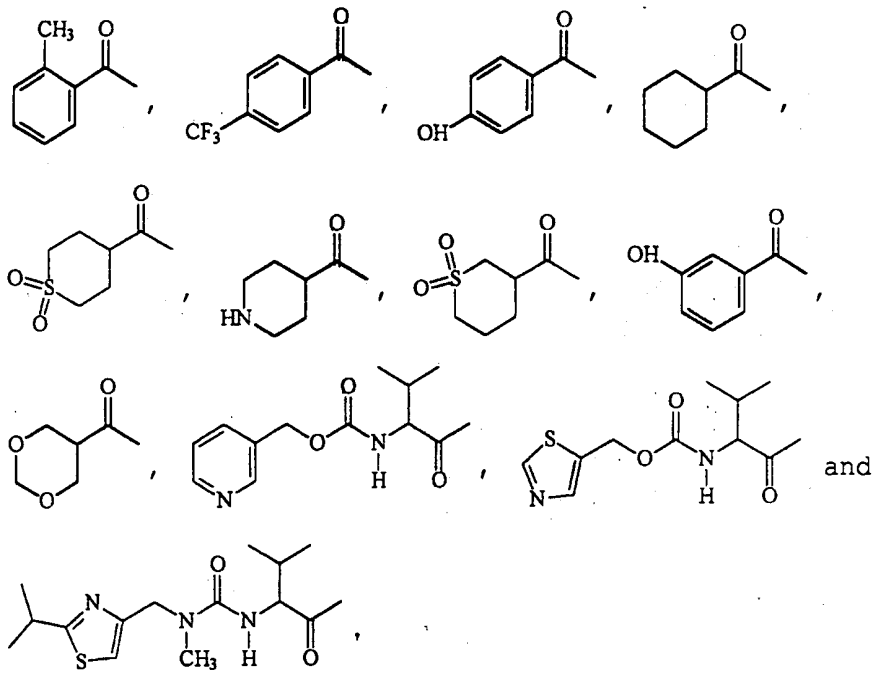
Other preferred compounds of formula VI include those compounds of formula LVIIa:

Formula LVIIa:



(LVIIa)

wherein A is selected from the group consisting of $-R^1$-Ht and $-R^1$-C_1-C_6 alkyl substituted with $-N(R^2)$-CO-$N(R^2)(R^2)$ or $-N(R^2)$-CO-O-R^2; R^1 is selected from the group consisting of -C(O)- and -O-C(O)-; and the other variables are defined as above for the compounds of formula I. For compounds of formula LVIIa, preferred definitions for A include $-R^1$-phenyl-R^7, $-R^1$-heterocycle and -Val-R^1-R^2. More preferred definitions for A include:

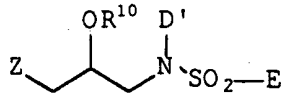


and

Preferred D and D' for compounds of formula LVIIa include C_1-C_6 alkyl, which may be optionally substituted with R^6.

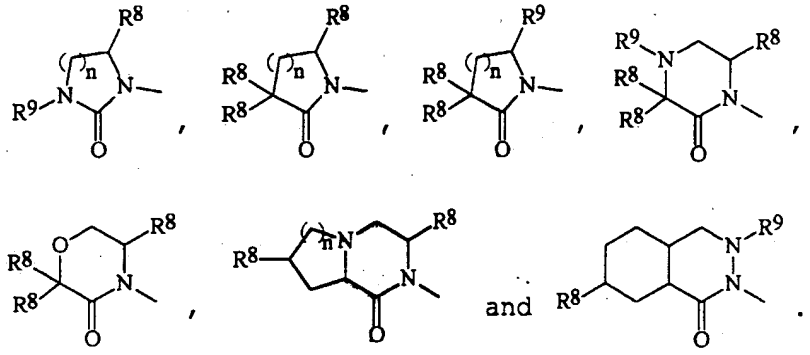
Preferred compounds of formula CIII also include those compounds having the formula LVIIb:

Formula LVIIb:



(LVIIb)

wherein Z is selected from the group consisting of:



and wherein R^8 is selected from the group consisting of R^2, -N-C(O)-O-R^2 and -N-C(O)-R^2; R^9 is selected from the group consisting of R^2, -C(O)-O-R^2 and -C(O)-R^2 and R^2 is as defined above for compounds of formula I.

For compounds of formula LVIIb, preferred D and D' are C_1-C_6 alkyl which may be optionally substituted with R^6.

Preferred compounds of formula VII include those compounds having the following definitions for one or more of the below-specified variables:

each D and D' is C_1-C_6 alkyl, which may be optionally substituted with R^6;

G is H_2;

one of X and X' is -OR^{10} and the other of X and X' is H;

each E' is independently selected from C_5-C_6 aryl, which may be optionally substituted with R^4;

each R^1 is selected from the group consisting of -C(O)- and -O-C(O)-;

each R^4 is independently selected from the group consisting of -OR^2, -N(R^2)(R^2) and -NO_2;

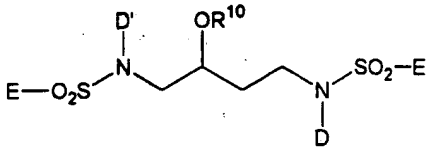
each Z is selected from the group consisting of -N(H)Ht; -N(H)A; -N(D)SO_2E; -N(D)A and -Ht; and more preferably from either -N(D)SO_2E or -N(H)Ht;

each Ht is independently selected from the group consisting of C_6-C_{10} aryl and 5-10 membered saturated or unsaturated heterocycle, and wherein any member of said Ht may be optionally substituted with one or more substituents, the same or different, selected from the group consisting of $-OR^2$, R^2, $-N(R^2)(R^2)$, $-NO_2$, $-C(O)N(R^2)(R^2)$, $-S(O)_n-R^6$, $-OR^{10}$, $-SR^{10}$, $-R^{10}$, $-N(R^2)(R^{10})$ and $-N(R^{10})_2$; and

each A is selected from the group consisting of H; $-R^1$-Ht and $-R^1$-C_1-C_6 alkyl.

Other preferred compounds of formula VII are those compounds having the structure of formula CIV:

Formula CIV:

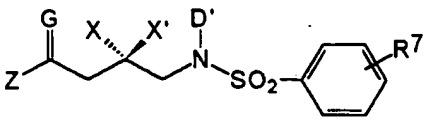


(CIV)

wherein the variables are defined as above for the compounds of formula VII.

Still other preferred compounds of formula VII are those compounds having the structure of formula LXII:

Formula LXII:



(LXII)

wherein one of X and X' is $-OR^{10}$ and the other of X and X' is H, and the remaining variables are defined as above for compounds of formula I and R^7 is selected from the group consisting of H, -OH, $-OR^2$, $-R^2$, $-N(R^2)(R^2)$, $-N(R^2)-C(O)-R^2$, $-R^2-OH$, -CN, $-CO_2R^2$, $-C(O)-N(R^2)(R^2)$, halo and $-CF_3$. Preferred compounds of formula LXII include those compounds having one or more variables as defined for preferred compounds of formula VII.

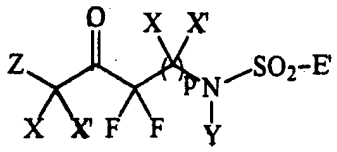
Preferred compounds of formula C include those compounds having each Z is selected from the group consisting of -N(H)Ht; -N(H)A; -N(D)A and -Ht; and one or more variables as defined for preferred compounds of formula VI.

More preferred compounds of formula C include those compounds wherein G is H_2, one of X and X' is $-OR^{10}$ and the other of X and X' is H.

Preferred compounds of formula CI include those compounds wherein X is a C_1 alkyl substituted with R^6 and D' is a C_1-C_4 alkyl optionally substituted with R^6. Most preferably, X is benzyl and D' is i-Bu or cyclopentylmethyl.

Preferred compounds of formula II include those compounds wherein X and X' on the carbon adjacent to the backbone carbon bearing Z, taken together, are oxygen. Other preferred compounds of formula II are those compounds having the structure of formula VIII:

Formula VIII:



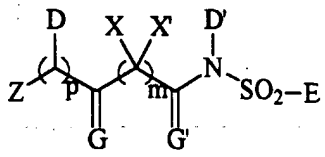
(VIII)

wherein the variables are as defined above for compounds of formula II.

Preferred compounds of formula VIII include those compounds wherein one or more of the variables are defined as follows; on the backbone carbon bearing Z, X is H and X' is D; on the backbone carbon adjacent to N-Y, X and X' are independently selected from D, and preferably from C_1-C_6 alkyl and H, and most preferably both are H; Y is selected from D, preferably from C_1-C_6 alkyl and H; and E is a C_6-C_{10} aryl optionally substituted with one or two substituents, the same or different, selected from -OH, $-OCH_3$ and $-NH_2$ and Z is selected from (3S)-THF-OC(O)NH- or 5-(1,3-dioxanyl)-OC(O)NH-.

In an alternative embodiment, the sulfonamides of this invention are those of formulas I', II' and III':

Formula I':



(I')

wherein:

each D and D' is independently selected from the group consisting of A^r; C_1-C_6 alkyl, which may be optionally substituted with one or more groups selected from C_3-C_6 cycloalkyl, $-OR^2$, $-R^3$, $-O-A^r$ and A^r; C_2-C_4 alkenyl, which may be optionally substituted with one or more groups selected from the group consisting of C_3-C_6 cycloalkyl, $-OR^2$, $-R^3$, $-O-A^r$ and A^r; C_3-C_6 cycloalkyl, which may be optionally substituted with or fused with A^r; and C_5-C_6 cycloalkenyl, which may be optionally substituted with or fused with A^r;

each A^r is independently selected from the group consisting of phenyl; 3-6 membered carbocyclic ring and 5-10 membered heterocyclic ring containing one or more heteroatoms selected from the group consisting of O, N, S, $S(O)_n$ and $N(R^2)$, wherein said carbocyclic or heterocyclic ring may be saturated or unsaturated and optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^2$, $-R^2$, $-N(R^2)(R^2)$, $-N(R^2)-C(O)-R^2$, $-R^2-OH$, $-CN$, $-CO_2R^2$, $-C(O)-N(R^2)(R^2)$, halo and $-CF_3$;

each R^2 is independently selected from the group consisting of H and C_1-C_4 alkyl optionally substituted with phenyl, 3-6 membered carbocyclic ring and 5-10 membered heterocyclic ring containing one or more heteroatoms selected from the group consisting of O, N, S and $S(O)_n$, wherein said carbocyclic or heterocyclic ring may be saturated or unsaturated and optionally substituted with one or more groups selected from the group consisting of OH, NH_2, CN, C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen and CF_3;

each R^3 is independently selected from the group consisting of H, Ht, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_6

cycloalkyl and C_5-C_6 cycloalkenyl, wherein any member of said R^3, except H, may be optionally substituted with one or more substituents selected from the group consisting of $-OR^2$, $-C(O)-NH-R^2$, $-S(O)_n-$, $N(R^2)(R^2)$, Ht, $-CN$, $-SR^2$, $-CO_2R^2$ and $NR^2-C(O)-R^2$;

each Ht is independently selected from the group consisting of C_3-C_7 cycloalkyl; C_5-C_7 cycloalkenyl; C_6-C_{10} aryl; and 5-10 membered saturated or unsaturated heterocycle, containing one or more heteroatoms selected from the group consisting of N, $N(R^2)$, O, S and $S(O)_n$, wherein said heterocycle may optionally be benzofused; wherein said heterocycle may be bicyclic or monocyclic; and wherein any member of said Ht may be optionally substituted with one or more substituents selected from the group consisting of oxo, $-OR^2$, $-R^2$, $-N(R^2)(R^2)$, $-R^2-OH$, $-CN$, $-CO_2R^2$, $-C(O)-N(R^2)(R^2)$, $-S(O)_2-N(R^2)(R^2)$, $-N(R^2)-C(O)-R^2$, $-C(O)-R^2$, $-S(O)_n-R^2$, $-OCF_3$, $-S(O)_n-A^r$, methylenedioxy, $-N(R^2)-S(O)_2(R^2)$, halo, $-CF_3$, $-NO_2$, A^r, $-O-A^r$, $-C(O)-N(D)(D)$, $-C(O)-N(H)D$, $-S(O)_n-D$, $-OR^{10}$, $-SR^{10}$, $-R^{10}$, $-N-(R^2)(R^{10})$, and $-N-(R^{10})_2$;

each E is independently selected from the group consisting of Ht; O-Ht; Ht-Ht; $-O-R^3$; $-NR^2R^3$; C_1-C_6 alkyl, which may be optionally substituted with one or more groups selected from the group consisting of R^{10}, R^4, and Ht; C_2-C_6 alkenyl, which may be optionally substituted with one or more groups selected from the group consisting of R^4, R^{10} and Ht; C_3-C_6 saturated monocyclic carbocycle, which be optionally benzofused, and which may optionally be substituted with one or more groups selected from the group consisting of R^4, $-R^{10}$, and Ht; C_5-C_6 unsaturated carbocycle, which may optionally be substituted with one or more groups selected from the group consisting of R^4, R^{10}, and Ht;

C_8-C_{10} saturated bicyclic carbocycle, which may be optionally substituted with one or more groups selected from the group consisting of R^4, R^{10}, and Ht;

each R^4 is independently selected from the group consisting of $-OR^2$, $-C(O)-NHR^2$, $-S(O)_2-NHR^2$, halo, $-NR^2-C(O)-R^2$, -CN, $-N(R^2)(R^2)$, $-NO_2$, $-C(O)N(D)(D)$ and $-C(O)N(H)D$;

each n is independently 1 or 2;

m is an integer selected from 1, 2 and 3;

p is an integer selected from 0 and 1;

G and G' are independently selected from the group consisting of H_2 and O;

one of X and X' is $-OR^{10}$ and the other of X and X' is H;

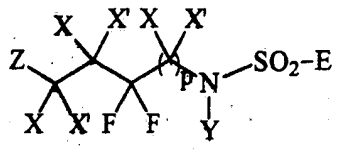
Z is selected from the group consisting of $-N(D)SO_2E$; $-N(D)SO_2Ht$; $-N(H)A$; $-N(D)A$; $-N(H)E$; $-N(H)C(O)N(D)(E)$; $-N(H)-Ht$; -Ht and $-N(D)-Ht$;

each A is independently selected from the group consisting of H; Ht; $-R^1-Ht$; $-R^1-C_1-C_6$ alkyl, which may be optionally substituted with one or more groups selected from the group consisting of hydroxy, R^{10}, C_1-C_4 alkoxy, Ht, -O-Ht, $-NR^2-CO-N(R^2)(R^2)$ and $-CO-N(R^2)(R^2)$; and $-R^1-C_2-C_6$ alkenyl, which may be optionally substituted with one or more groups selected from the group consisting of hydroxy, R^{10}, C_1-C_4 alkoxy, Ht, -O-Ht, $-NR^2-CO-N(R^2)(R^2)$ and $-CO-N(R^2)(R^2)$;

each R^1 is independently selected from the group consisting of $-C(O)-$, $-S(O)_2-$, $-C(O)-C(O)-$, $-O-C(O)-$, $-O-S(O)_2$, $-NR^2-S(O)_2-$, $-NR^2-C(O)-$ and $-NR^2-C(O)-C(O)-$; and

each R^{10} is as defined for compounds of formula I.

Formula II':



II'

wherein:

each E is independently selected from the group consisting of Ht; O-Ht; Ht-Ht; $-O-R^3$; $-NR^2R^3$; C_1-C_6 alkyl, which may be optionally substituted with one or more groups selected from the group consisting of R^{10}, R^4, and Ht; C_2-C_6 alkenyl, which may be optionally substituted with one or more groups selected from the group consisting of R^{10}, R^4, and Ht; C_3-C_6 saturated monocyclic carbocycle, which be optionally benzofused, and which may optionally be substituted with one or more groups selected from the group consisting of R^{10}, R^4, and Ht; C_5-C_6 unsaturated carbocycle, which may optionally be substituted with one or more groups selected from the group consisting of R^{10}, R^4, and Ht; C_8-C_{10} saturated bicyclic carbocycle, which may be optionally substituted with one or more groups selected from the group consisting of R^{10}, R^4, and Ht;

each R^4 is independently selected from the group consisting of $-OR^2$, $-C(O)-NHR^2$, $-S(O)_2-NHR^2$, halo, $-NR^2-C(O)-R^2$, -CN, -C(O)N(D)(D) and -C(O)N(H)D;

p is an integer selected from 0 and 1;

each Y is independently selected from the group consisting of hydrogen and D;

each D is independently selected from the group consisting of A^r; C_1-C_6 alkyl, which may be optionally substituted with one or more groups selected from the group consisting of C_3-C_6 cycloalkyl, $-OR^2$, $-R^3$, $-O-A^r$ and A^r; C_2-C_4 alkenyl, which may be optionally substituted with one or more groups selected from the group consisting of C_3-C_6 cycloalkyl, $-OR^2$, $-R^3$, $-O-A^r$ and A^r; C_3-C_6 cycloalkyl, which may be optionally substituted with or fused with A^r; and C_5-C_6 cycloalkenyl, which may be optionally substituted with or fused with A^r;

each A^r is independently selected from the group consisting of phenyl; 3-6 membered carbocyclic ring and 5-10 membered heterocyclic ring containing one or more heteroatoms selected from the group consisting of O, N, S, $S(O)_n$ and $N(R^2)$, wherein said carbocyclic or heterocyclic ring may be saturated or unsaturated and optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^2$, $-R^2$, $-N(R^2)(R^2)$, $-N(R^2)-C(O)-R^2$, $-R^2-OH$, $-CN$, $-CO_2R^2$, $-C(O)-N(R^2)(R^2)$, halo and $-CF_3$;

each R^2 is independently selected from the group consisting of H and C_1-C_4 alkyl optionally substituted with phenyl, 3-6 membered carbocyclic ring and 5-10 membered heterocyclic ring containing one or more heteroatoms selected from the group consisting of O, N, S and $S(O)_n$, wherein said carbocyclic or heterocyclic ring may be saturated or unsaturated and optionally substituted with one or more groups selected from the group consisting of OH, NH_2, CN, C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen and CF_3;

each R^3 is independently selected from the group consisting of H, Ht, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_6

cycloalkyl and C_5-C_6 cycloalkenyl, wherein any member of said R^3, except H, may be optionally substituted with one or more substituents selected from the group consisting of $-OR^2$, $-C(O)-NH-R^2$, $-S(O)_n-N(R^2)(R^2)$, Ht, $-CN$, $-SR^2$, $-CO_2R^2$ and $NR^2-C(O)-R^2$;

each Ht is independently selected from the group consisting of C_3-C_7 cycloalkyl; C_5-C_7 cycloalkenyl; C_6-C_{10} aryl; and 5-10 membered saturated or unsaturated heterocycle, containing one or more heteroatoms selected from the group consisting of N, $N(R^2)$, O, S and $S(O)_n$, wherein said heterocycle may optionally be benzofused; wherein said heterocycle may be bicyclic or monocyclic; and wherein any member of said Ht may be optionally substituted with one or more substituents selected from the group consisting of oxo, $-OR^2$, $-R^2$, $-N(R^2)(R^2)$, $-R^2-OH$, $-CN$, $-CO_2R^2$, $-C(O)-N(R^2)(R^2)$, $-S(O)_2-N(R^2)(R^2)$, $-N(R^2)-C(O)-R^2$, $-C(O)-R^2$, $-S(O)_n-R^2$, $-OCF_3$, $-S(O)_n-A^r$, methylenedioxy, $-N(R^2)-S(O)_2(R^2)$, halo, $-CF_3$, $-NO_2$, A^r, $-O-A^r$, $-C(O)-N(D)(D)$, $-C(O)N(H)D$, $-S(O)_n-D$, $-OR^{10}$, $-SR^{10}$, $-R^{10}$, $-N(R^2)(R^{10})$ and $-N(R^2)_2$;

each n is independently 1 or 2;

each Z is independently selected from the group consisting of $-N(D)SO_2E$; $-N(D)SO_2Ht$; $-N(H)A$; $-N(D)A$; $-N(H)E$; $-N(H)C(O)N(D)(E)$; $-N(H)-Ht$; $-Ht$ and $-N(D)-Ht$;

each A is independently selected from the group consisting of H; Ht; $-R^1-Ht$; $-R^1-C_1-C_6$ alkyl, which may be optionally substituted with one or more groups selected from the group consisting of hydroxy, C_1-C_4 alkoxy, Ht and $-O-Ht$, $-NR^2-CO-N(R^2)(R^2)$ and $-CO-N(R^2)(R^2)$; and $-R^1-C_2-C_6$ alkenyl, which may be optionally substituted with one or more groups selected from the group consisting of hydroxy, C_1-C_4 alkoxy, Ht, $-O-Ht$, $-R^{10}$, $-NR^2-CO-N(R^2)(R^2)$ and $-CO-N(R^2)(R^2)$;

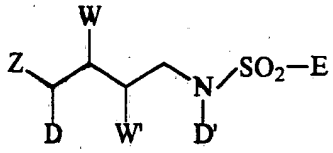
each R^1 is independently selected from the group consisting of $-C(O)-$, $-S(O)_2-$, $-C(O)-C(O)-$, $-O-C(O)-$, $-O-S(O)_2$, $-NR^2-S(O)_2-$, $-NR^2-C(O)-$ and $-NR^2-C(O)-C(O)-$;

each X and X' is independently selected from the group consisting of hydrogen; $-OH$; $-NH_2$; $-SH$; D and, if X and X' are taken together, oxygen;

provided that at least one X or X' is $-OR^{10}$ and the other geminal X' or X, respectively, is H; and

each R^{10} is as defined for compounds of formula I.

Formula III':



III'

wherein:

each D and D' is independently selected from the group consisting of A^r; C_1-C_6 alkyl, which may be optionally substituted with one or more groups selected from the group consisting of C_3-C_6 cycloalkyl, $-OR^2$, $-R^3$, $-O-A^r$ and A^r; C_2-C_4 alkenyl, which may be optionally substituted with one or more groups selected from the group consisting of C_3-C_6 cycloalkyl, $-OR^2$, $-R^3$, $-O-A^r$ and A^r; C_3-C_6 cycloalkyl, which may be optionally substituted with or fused with A^r; and C_5-C_6 cycloalkenyl, which may be optionally substituted with or fused with A^r;

each A^r is independently selected from the group consisting of phenyl; 3-6 membered carbocyclic ring and

5-10 membered heterocyclic ring containing one or more heteroatoms selected from the group consisting of O, N, S, $S(O)_n$ and $N(R^2)$, wherein said carbocyclic or heterocyclic ring may be saturated or unsaturated and optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^2$, $-R^2$, $-N(R^2)(R^2)$, $-N(R^2)-C(O)-R^2$, $-R^2-OH$, $-CN$, $-CO_2R^2$, $-C(O)-N(R^2)(R^2)$, halo and $-CF_3$;

each R^2 is independently selected from the group consisting of H and C_1-C_4 alkyl optionally substituted with phenyl, 3-6 membered carbocyclic ring and 5-10 membered heterocyclic ring containing one or more heteroatoms selected from the group consisting of O, N, S and $S(O)_n$, wherein said carbocyclic or heterocyclic ring may be saturated or unsaturated and optionally substituted with one or more groups selected from the group consisting of OH, NH_2, CN, C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen and CF_3;

each R^3 is independently selected from the group consisting of H, Ht, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkyl and C_5-C_6 cycloalkenyl, wherein any member of said R^3, except H, may be optionally substituted with one or more substituents selected from the group consisting of $-OR^2$, $-C(O)-NH-R^2$, $-S(O)_n-N(R^2)(R^2)$, Ht, $-CN$, $-SR^2$, $-CO_2R^2$ and $NR^2-C(O)-R^2$;

each Ht is independently selected from the group consisting of C_3-C_7 cycloalkyl; C_5-C_7 cycloalkenyl; C_6-C_{10} aryl; and 5-10 membered saturated or unsaturated heterocycle, containing one or more heteroatoms selected from the group consisting of N, $N(R^2)$, O, S and $S(O)_n$, wherein said heterocycle may optionally be benzofused; wherein said heterocycle may bicyclic or monocyclic; and wherein any member of said Ht may be

optionally substituted with one or more substituents selected from the group consisting of oxo, $-OR^2$, $-R^2$, $-N(R^2)(R^2)$, $-R^2-OH$, $-CN$, $-CO_2R^2$, $-C(O)-N(R^2)(R^2)$, $-S(O)_2-N(R^2)(R^2)$, $-N(R^2)-C(O)-R^2$, $-C(O)-R^2$, $-S(O)_n-R^2$, $-OCF_3$, $-S(O)_n-A^r$, methylenedioxy, $-N(R^2)-S(O)_2(R^2)$, halo, $-CF_3$, $-NO_2$, A^r, $-O-A^r$, $-C(O)-N(D)(D)$, $-C(O)N(H)D$, $-S(O)_n-D$, $-OR^{10}$, $-SR^{10}$, $-R^{10}$, $-N(R^2)(R^{10})$ and $-N(R^{10})_2$; and

each E is independently selected from the group consisting of Ht; O-Ht; Ht-Ht; $-O-R^3$; $-NR^2R^3$; C_1-C_6 alkyl, which may be optionally substituted with one or more groups selected from the group consisting of R^4 and Ht; C_2-C_6 alkenyl, which may be optionally substituted with one or more groups selected from the group consisting of $-OR^{10}$, R^4 and Ht; C_3-C_6 saturated monocyclic carbocycle, which be optionally benzofused, and which may optionally be substituted with one or more groups selected from the group consisting of $-OR^{10}$, R^4 and Ht; C_5-C_6 unsaturated carbocycle, which may optionally be substituted with one or more groups selected from the group consisting of $-OR^{10}$, R^4 and Ht; C_8-C_{10} saturated bicyclic carbocycle, which may be optionally substituted with one or more groups selected from the group consisting of $-OR^{10}$, R^4 and Ht; and

each R^4 is independently selected from the group consisting of $-OR^2$, $-C(O)-NHR^2$, $-S(O)_2-NHR^2$, halo, $-NR^2-C(O)-R^2$, $-CN$, $-C(O)-N(D)(D)$ and $-C(O)-N(H)D$;

each n is independently 1 or 2;

W and W' are independently selected from the group consisting of hydrogen, D , -OH and $-OR^{10}$, provided that at least one of W and W' is $-OR^{10}$;

each Z is independently selected from the group consisting of $-N(D)SO_2E$; $-N(D)SO_2Ht$; $-N(H)A$; $-N(D)A$; $-N(H)E$; $-N(H)C(O)N(D)(E)$; $-N(H)-Ht$; $-Ht$ and $-N(D)-Ht$;

each A is independently selected from the group consisting of H; Ht; -R^1-Ht; -R^1-C_1-C_6 alkyl, which may be optionally substituted with one or more groups selected from the group consisting of hydroxy, -OR^{10}, C_1-C_4 alkoxy, Ht, -O-Ht, -NR^2-CO-N(R^2)(R^2) and -CO-N(R^2)(R^2); and -R^1-C_2-C_6 alkenyl, which may be optionally substituted with one or more groups selected from the group consisting of hydroxy, C_1-C_4 alkoxy, Ht, -O-Ht, -NR^2-CO-N(R^2)(R^2) and -CO-N(R^2)(R^2);

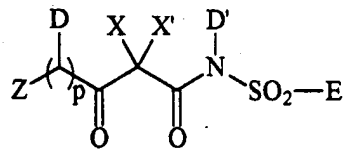
each R^1 is independently selected from the group consisting of -C(O)-, -$S(O)_2$-, -C(O)-C(O)-, -O-C(O)-, -O-$S(O)_2$, -NR^2-$S(O)_2$-, -NR^2-C(O)- and -NR^2-C(O)-C(O)-; and

each R^{10} is as defined for compounds of formula I.

Except where expressly noted to the contrary, the term for any given variable, the term "[variable] as defined for formulas I', II' or III'" refers to the definitions shown directly above.

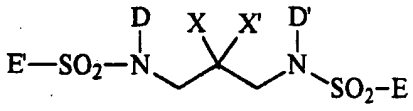
Other preferred compounds of formula I' include those compounds having the structures of formulas IV', V', VI', VII', LXIII' and LXIV':

Formula IV':



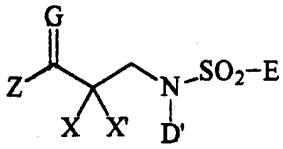
IV'

Formula V':



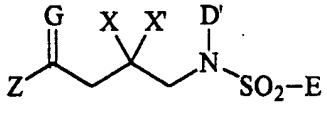
V'

Formula VI':



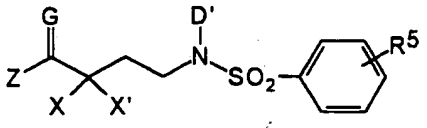
VI'

Formula VII':



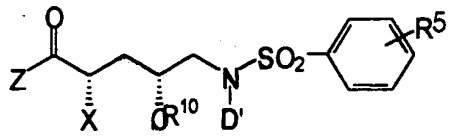
VII'

Formula LXIII':



(LXIII')

Formula LXIV':



(LXIV')

wherein D, D', A^r, R^1, R^2, R^3, Ht, E, E', R^4, R^{10}, n, m, p, G, G', Z and A are as defined for the compounds of formula I' and R^5 is selected from the group consisting of H, -OH, $-OR^2$, $-R^2$, $-N(R^2)(R^2)$, $-N(R^2)-C(O)-R^2$, $-R^2-OH$, -CN, $-CO_2R^2$, $-C(O)-N(R^2)(R^2)$, halo and $-CF_3$; and one of X and X' is $-OR^{10}$ and the other of X and X', if present, is H. Unless expressly noted to the contrary, the term for any given variable, the term "[variable] as defined for formula IV', V', VI', VII', LXIII' or LXIV'" refers to the definitions shown directly above.

Preferred compounds of formula IV' include those compounds wherein:

each D and D' is independently selected from the group consisting of C_1-C_6 alkyl, which may be optionally substituted with one or more groups selected from the group consisting of C_3-C_6 cycloalkyl and A^r;

each A^r is independently selected from the group consisting of phenyl; 3-6 membered carbocyclic ring and 5-10 membered heterocyclic ring containing one or more heteroatoms selected from the group consisting of O, N, S, $S(O)_n$ and $N(R^2)$, wherein said carbocyclic or heterocyclic ring may be saturated or unsaturated and optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^2$, $-R^2$, $-N(R^2)(R^2)$,

$-N(R^2)-C(O)-R^2$, $-R^2-OH$, $-CN$, $-CO_2R^2$, $-C(O)-N(R^2)(R^2)$, halo and $-CF_3$;

each R^2 is independently selected from the group consisting of H and C_1-C_4 alkyl optionally substituted with phenyl, 3-6 membered carbocyclic ring and 5-10 membered heterocyclic ring containing one or more heteroatoms selected from the group consisting of O, N, S and $S(O)_n$, wherein said carbocyclic or heterocyclic ring may be saturated or unsaturated and optionally substituted with one or more groups selected from the group consisting of OH, NH_2, CN, C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen and CF_3;

each E is independently selected from C_5-C_6 unsaturated carbocycle, which may be optionally substituted with one or more R^4;

each R^4 is independently selected from the group consisting of $-OR^2$, $-N(R^2)(R^2)$ and $-NO_2$;

each Z is independently selected from the group consisting of $-N(D)SO_2E$; $-N(D)SO_2Ht$; $-N(H)Ht$; $-N(H)A$; $-N(D)A$ and $-Ht$;

each Ht is independently selected from the group consisting of C_6-C_{10} aryl and 5-10 membered saturated or unsaturated heterocycle, containing one or more heteroatoms selected from the group consisting of N, $N(R^2)$, O, S, and $S(O)_n$, wherein said heterocycle may optionally be benzofused; wherein said heterocycle may be bicyclic or monocyclic; and wherein any member of said Ht may be optionally substituted with one or more substituents selected from the group consisting of $-OR^2$, R^2, $-N(R^2)(R^2)$, $-NO_2$, $-C(O)N(R^2)(R^2)$, $-S(O)_n-A^r$, $-OR^{10}$, $-SR^{10}$, $-R^{10}$, $-N(R^2)(R^{10})$, and $-N(R^{10})_2$;

each A is independently selected from the group consisting of H; $-R^1$-Ht and $-R^1$-C_1-C_6 alkyl; and

each R^1 is independently selected from the group consisting of $-C(O)-$, $-S(O)_2-$, $-C(O)-C(O)-$, $-O-C(O)-$, $-O-S(O)_2$, $-NR^2-S(O)_2-$, $-NR^2-C(O)-$ and $-NR^2-C(O)-C(O)-$.

Preferred compounds of formula VI' include those compounds wherein:

each D and D' is independently selected from the group consisting of C_1-C_6 alkyl, which may be optionally substituted with one or more groups selected from the group consisting of C_3-C_6 cycloalkyl and A^r;

each E is independently selected from C_5-C_6 unsaturated carbocycle, which may be optionally substituted with one or more R^4;

each R^4 is independently selected from the group consisting of $-OR^2$, $-N(R^2)(R^2)$ and $-NO_2$;

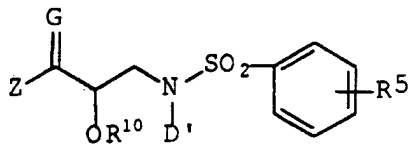
Z is selected from the group consisting of $-N(D)SO_2E$; $-N(D)SO_2Ht$; $-N(H)Ht$; $-N(H)A$; $-N(D)A$ and $-Ht$;

each Ht is independently selected from the group consisting of C_6-C_{10} aryl and 5-10 membered saturated or unsaturated heterocycle, containing one or more heteroatoms selected from the group consisting of N, $N(R^2)$, O, S, and $S(O)_n$, wherein said heterocycle may optionally be benzofused; wherein said heterocycle may be bicyclic or monocyclic; and wherein any member of said Ht may be optionally substituted with one or more substituents selected from the group consisting of $-OR^2$, R^2, $-N(R^2)(R^2)$, $-NO_2$, $-C(O)N(R^2)(R^2)$, $-S(O)_n-A^r$, $-OR^{10}$, $-SR^{10}$, $-R^{10}$, $-N(R^2)(R^{10})$, and $-N(R^{10})_2$; and

A is selected from the group consisting of H; $-R^1-Ht$ and $-R^1-C_1$-C_6 alkyl.

Other preferred compounds of formula VI' include those compounds of formula LVII':

Formula LVII':



(LVII')

wherein D, D', A^r, R^1, R^2, R^3, R^{10}, Ht, E, R^4, G, n, Z and A are defined as above for the compounds of formula VI' and R^5 is selected from the group consisting of H, -OH, $-OR^2$, $-R^2$, $-N(R^2)(R^2)$, $-N(R^2)-C(O)-R^2$, $-R^2-OH$, -CN, $-CO_2R^2$, $-C(O)-N(R^2)(R^2)$, halo and $-CF_3$.

Preferred compounds of formula VII' include those compounds wherein:

each D and D' is C_1-C_6 alkyl, which may be optionally substituted with one or more groups selected from the group consisting of C_3-C_6 cycloalkyl and A^r;

each E is independently selected from C_5-C_6 unsaturated carbocycle, which may be optionally substituted with one or more R^4;

each R^4 is independently selected from the group consisting of $-OR^2$, $-N(R^2)(R^2)$ and $-NO_2$;

Z is selected from the group consisting of $-N(D)SO_2E$; $-N(D)SO_2Ht$; $-N(H)Ht$; $-N(H)A$; $-N(D)A$ and -Ht;

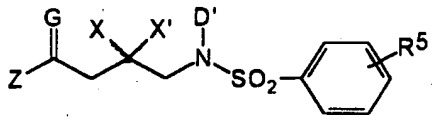
each Ht is independently selected from the group consisting of C_6-C_{10} aryl and 5-10 membered saturated or unsaturated heterocycle, containing one or more heteroatoms selected from the group consisting of N, $N(R^2)$, O, S, and $S(O)_n$, wherein said heterocycle may optionally be benzofused; wherein said heterocycle may be bicyclic or monocyclic; and wherein any member of

said Ht may be optionally substituted with one or more substituents selected from the group consisting of $-OR^2$, R^2, $-N(R^2)(R^2)$, $-NO_2$, $-C(O)N(R^2)(R^2)$, $-S(O)_n-A^r$, $-OR^{10}$, $-SR^{10}$, $-R^{10}$, $-N(R^2)(R^{10})$, and $-N(R^{10})_2$; and

A is selected from the group consisting of H; $-R^1$-Ht and $-R^1-C_1-C_6$ alkyl.

Other preferred compounds of formula VII' are those compounds having the structure of formula LXII':

Formula LXII':

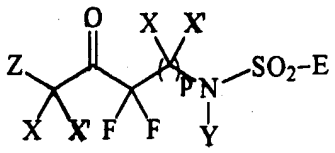


(LXII')

wherein one of X and X' is $-OR^{10}$ and the other of X and X' is H; and D, D', A^r, R^1, R^2, R^3, Ht, E, R^4, G, n, Z and A are defined as above for the compounds of formula VII' and R^5 is selected from the group consisting of H, -OH, $-OR^2$, $-R^2$, $-N(R^2)(R^2)$, $-N(R^2)-C(O)-R^2$, $-R^2$-OH, -CN, $-CO_2R^2$, $-C(O)-N(R^2)(R^2)$, $-OR^{10}$, halo and $-CF_3$.

Preferred compounds of formula II' include those compounds wherein X and X' on the carbon adjacent to the carbon bearing Z on the backbone, taken together, are oxygen. Other preferred compounds of formula II' are those compounds having the structure of formula VIII':

Formula VIII':



VIII'

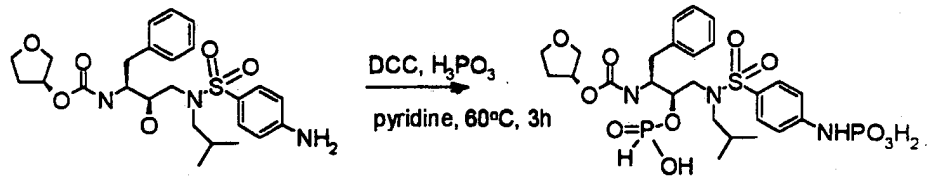
wherein one of X and X' is $-OR^{10}$ and the other of X and X' is H; and E, R^1, R^2, R^3, R^4, n, p, Y, D, A^r, Ht, Z and A, are as defined above for compounds of formula II'. Except where expressly noted to the contrary, the term for any given variable, the term "[variable] defined as for a compound of formula VIII'" refers to the definition directly above.

The prodrugs of the present invention may be synthesized using conventional synthetic techniques. WO 95/24385 discloses the synthesis of compounds which are precursors of the prodrugs of the present application.

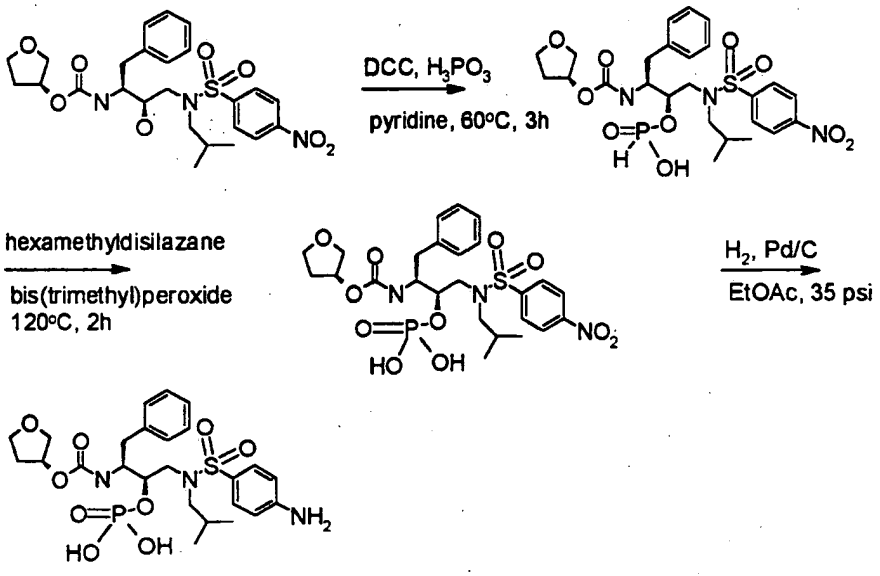
Prodrugs of formula (I) of the present invention can be readily synthesized from the '385 compounds using conventional techniques. One of skill in the art would be well aware of conventional synthetic reagents to convert the -OH group of the '385 compounds to a desired $-OR^{10}$ functionality of the present invention, wherein R^{10} is as defined above. The relative ease with which the compounds of this invention can be synthesized represents an enormous advantage in the large scale production of these compounds.

For example, VX-478, a compound disclosed in the United States patent 5,585,397, can be readily

converted to the corresponding bis-phosphate ester derivative, as shown below:



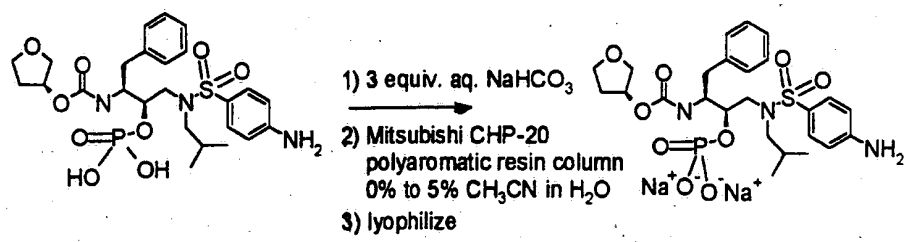
Alternatively, if the monophosphate ester of VX-478 is desired, then the synthetic scheme can be readily adapted by beginning with the 4-nitrophenyl derivative of VX-478, as shown below:



The prodrugs of the present invention can be synthesized by analogous reactions using the compounds WO 95/24385.

Pharmaceutically acceptable salts of the compounds of the present invention may be readily prepared using known techniques. For example, the

disodium salt of the mono-phosphate ester shown above can be prepared as shown below:



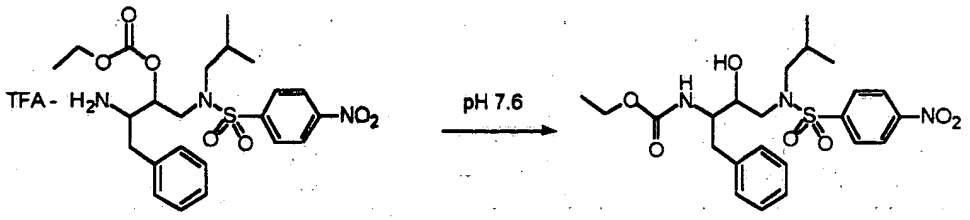
This synthetic methodology can be readily extended to prepare phosphate ester prodrugs of the present invention.

The compounds of this invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

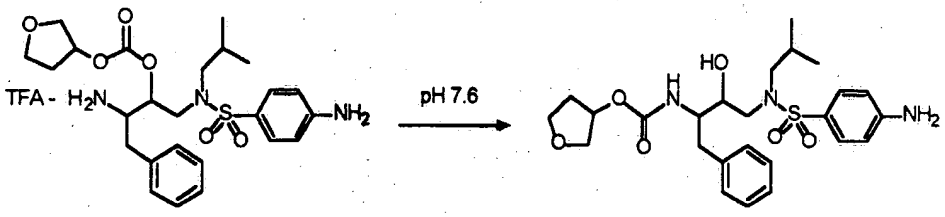
Without being bound by theory, we believe that two different mechanisms are involved in converting the prodrugs of this invention into the active drug, depending upon the structure of the prodrug. The first mechanism involves the enzymatic or chemical transformation of the prodrug species into the active form. The second mechanism involves the enzymatic or chemical cleavage of a functionality on the prodrug to produce the active compound.

The chemical or enzymatic transformation can involve the transfer of a functional group (i.e., R^7) from one heteroatom within the molecule to another

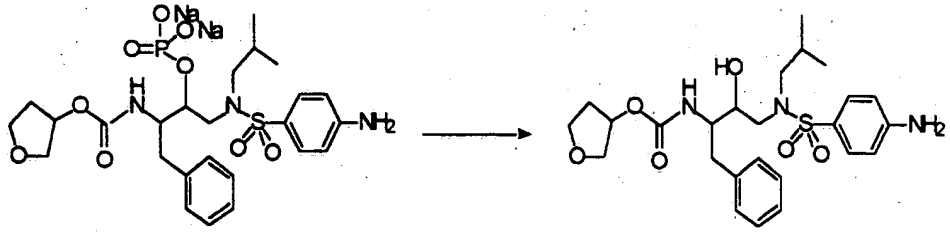
heteroatom. This transfer is demonstrated in the chemical reactions shown below:



and



The cleavage mechanism is demonstrated by the reaction below where a phosphate ester-containing prodrug is converted into the active form of the drug by removal of the phosphate group.



These protease inhibitors and their utility as inhibitors of aspartyl proteases are described in WO 95/24385, the disclosure of which is incorporated herein by reference.

The prodrugs of the present invention are characterized by unexpectedly high aqueous solubility. This solubility facilitates administration of higher doses of the prodrug, resulting in a greater drug load per unit dosage. The prodrugs of the present invention are also characterized by facile hydrolytic cleavage to release the active aspartyl protease inhibitor in vivo. The high aqueous solubility and the facile in vivo metabolism result in a greater bioavailability of the drug. As a result, the pill burden on a patient is significantly reduced.

The prodrugs of this invention may be employed in a conventional manner for the treatment of viruses, such as HIV and HTLV, which depend on aspartyl proteases for obligatory events in their life cycle. Such methods of treatment, their dosage levels and requirements may be selected by those of ordinary skill in the art from available methods and techniques. For example, a prodrug of this invention may be combined with a pharmaceutically acceptable adjuvant for administration to a virally-infected patient in a pharmaceutically acceptable manner and in an amount effective to lessen the severity of the viral infection.

Alternatively, the prodrugs of this invention may be used in vaccines and methods for protecting individuals against viral infection over an extended period of time. The prodrugs may be employed in such vaccines either alone or together with other compounds of this invention in a manner consistent with the conventional utilization of protease inhibitors in vaccines. For example, a prodrug of this invention may be combined with pharmaceutically acceptable adjuvants

conventionally employed in vaccines and administered in prophylactically effective amounts to protect individuals over an extended period of time against HIV infection. As such, the novel protease inhibitors of this invention can be administered as agents for treating or preventing HIV infection in a mammal.

The prodrugs of this invention may be administered to a healthy or HIV-infected patient either as a single agent or in combination with other anti-viral agents which interfere with the replication cycle of HIV. By administering the compounds of this invention with other anti-viral agents which target different events in the viral life cycle, the therapeutic effect of these compounds is potentiated. For instance, the co-administered anti-viral agent can be one which targets early events in the life cycle of the virus, such as cell entry, reverse transcription and viral DNA integration into cellular DNA. Anti-HIV agents targeting such early life cycle events include, didanosine (ddI), alcitabine (ddC), d4T, zidovudine (AZT), polysulfated polysaccharides, sT4 (soluble CD4), ganiclovir, dideoxycytidine, trisodium phosphonoformate, eflornithine, ribavirin, acyclovir, alpha interferon and trimenotrexate. Additionally, non-nucleoside inhibitors of reverse transcriptase, such as TIBO or nevirapine, may be used to potentiate the effect of the compounds of this invention, as may viral uncoating inhibitors, inhibitors of trans-activating proteins such as tat or rev, or inhibitors of the viral integrase.

Combination therapies according to this invention exert a synergistic effect in inhibiting HIV replication because each component agent of the

combination acts on a different site of HIV replication. The use of such combinations also advantageously reduces the dosage of a given conventional anti-retroviral agent which would be required for a desired therapeutic or prophylactic effect as compared to when that agent is administered as a monotherapy. These combinations may reduce or eliminate the side effects of conventional single anti-retroviral agent therapies while not interfering with the anti-retroviral activity of those agents. These combinations reduce potential of resistance to single agent therapies, while minimizing any associated toxicity. These combinations may also increase the efficacy of the conventional agent without increasing the associated toxicity. In particular, we have discovered that these prodrugs act synergistically in preventing the replication of HIV in human T cells. Preferred combination therapies include the administration of a prodrug of this invention with AZT, ddI, ddC or d4T.

Alternatively, the prodrugs of this invention may also be co-administered with other HIV protease inhibitors such as Ro 31-8959 (Roche), L-735,524 (Merck), XM 323 (Du-Pont Merck) and A-80,987 (Abbott) to increase the effect of therapy or prophylaxis against various viral mutants or members of other HIV quasi species.

We prefer administering the prodrugs of this invention as single agents or in combination with retroviral reverse transcriptase inhibitors, such as derivatives of AZT, or other HIV aspartyl protease inhibitors. We believe that the co-administration of the compounds of this invention with retroviral reverse

transcriptase inhibitors or HIV aspartyl protease inhibitors may exert a substantial synergistic effect, thereby preventing, substantially reducing, or completely eliminating viral infectivity and its associated symptoms.

The prodrugs of this invention can also be administered in combination with immunomodulators (e.g., bropirimine, anti-human alpha interferon antibody, IL-2, GM-CSF, methionine enkephalin, interferon alpha, diethyldithiocarbamate, tumor necrosis factor, naltrexone and rEPO); and antibiotics (e.g., pentamidine isethiorate) to prevent or combat infection and disease associated with HIV infections, such as AIDS and ARC.

When the prodrugs of this invention are administered in combination therapies with other agents, they may be administered sequentially or concurrently to the patient. Alternatively, pharmaceutical or prophylactic compositions according to this invention may be comprised of a combination of a prodrug of this invention and another therapeutic or prophylactic agent.

Although this invention focuses on the use of the prodrugs disclosed herein for preventing and treating HIV infection, the compounds of this invention can also be used as inhibitory agents for other viruses which depend on similar aspartyl proteases for obligatory events in their life cycle. These viruses include, as well as other AIDS-like diseases caused by retroviruses, such as simian immunodeficiency viruses, but are not limited to, HTLV-I and HTLV-II. In addition, the compounds of this invention may also be used to inhibit other aspartyl proteases, and in

particular, other human aspartyl proteases, including renin and aspartyl proteases that process endothelin precursors.

Pharmaceutical compositions of this invention comprise any of the compounds of the present invention, and pharmaceutically acceptable salts thereof, with any pharmaceutically acceptable carrier, adjuvant or vehicle. Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. We prefer oral administration or administration by injection. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous,

intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant such as Ph. Helv or a similar alcohol.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, and aqueous suspensions and solutions. In the case of tablets for oral use,

carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or

cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches are also included in this invention.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

Dosage levels of between about .01 and about 100 mg/kg body weight per day, preferably between about 0.5 and about 50 mg/kg body weight per day of the active ingredient compound are useful in the prevention and treatment of viral infection, including HIV infection. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about

95% active compound (w/w). Preferably, such preparations contain from about 20% to about 80% active compound.

Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level, treatment should cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

As the skilled artisan will appreciate, lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the infection, the patient's disposition to the infection and the judgment of the treating physician.

In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

Example 1

General conditions:

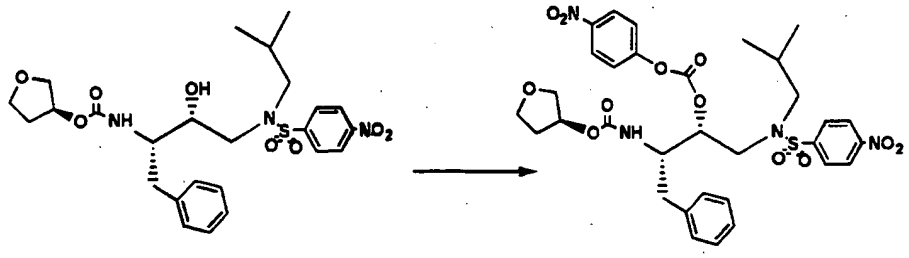
(A) Analytical HPLC 0-100%B/30 min, 1.5 mL/min, A=0.1% TFA in water, B=0.1% TFA in acetonitrile.

Detection at 254 and 220 nm, C18 reverse phase Vydac, t0=2.4 min.

(B) 1/3 v/v EtOAc/hexane

(C) 1/2 v/v EtOAc/hexane

(D) Analytical HPLC 0-100%B/10 min, 1.5 mL/min, A=0.1% TFA in water, B=0.1% TFA in acetonitrile. Detection at 254 and 220 nm, C18 reverse phase Vydac, t_0=2.4 min.



197 198

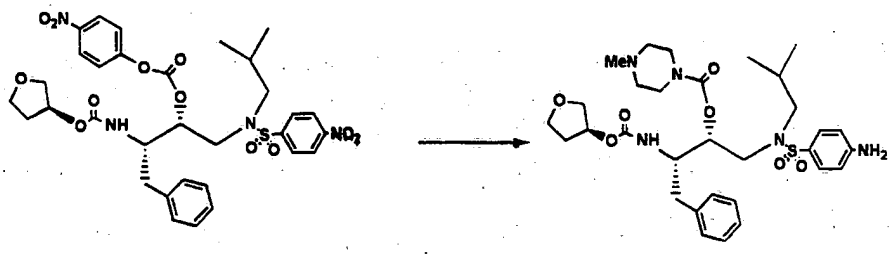
A mixture of 2.0g (3.7 mMol) of 197 and 3.0g (16 mMol) of di-p-nitrophenyl carbonate in 10 ml of dimethylformamide was treated at 25° with 4 ml (4 mMol) of P4-phosphazene base (Fluka, 1M in hexane). The mixture was stirred for 6h at 25° until all of the starting alcohol was consumed. The reaction mixture was partitioned between ethyl acetate and 1N hydrochloric acid. The organic layer was washed with 1N sodium hydroxide and brine, dried over magnesium sulfate and concentrated in vacuo. Titration with dichloromethane gave the desired mixed carbonate (1.2g crop1 and 0.6g crop 2) as a fine powder. Combined yield: 69%. Rf=0.13 (1/3 EtOAc/hexane, conditions B), Rf=0.40 (1/2 EtOAc/hexane, conditions C), tHPLC=23.83 min (A), MS(ES+) 701 (M+1).

1H-NMR (CDCl3): 0.82 (6H,dd), 1.9 (2H,m), 2.15 (1H,m), 2.8 (1H,m), 3.0 (4H,m), 3.5 (2H,m), 3.6 (1H,m), 3.8

(4H,m), 4.3 (1H,bs), 4,8 (1H,m), 5.17 (2H,m), 7.7 (7H,m), 7.95 (2H,d), 8.35 (4H,m).

13C (CDCl3): 155.2 152,2, 149.9, 145.6, 135.9, +129.0, +128.8, +128.5, +127.2, +125.4, +124.4, +121.8, +78.1, +75.8, -73.1, -66.9, -56.5, +52.7, -48.2, -35.9, -35.9, 32.6, -+26.4, +19.9, +19.8.

Example 2



198 199

To 0.20g (0.286 mM) of 198 dissolved in 3 ml of THF was added 0.11 g (1.14 mM) of 1-Methyl-piperidine and the mixture was stirred overnight at room temperature ("rt"). All the solvents were then evaporated and the solid residue partitioned between EtOAc and water. The volatiles were removed and, where appropriate, the residue was treated with 1:1 TFA/DCM over 30 min at rt to remove the Boc protecting group. The product was dissolved in 0.25 ml TFA and 1.5 ml THF. Hydrogenolysis for 10 hours in presence of 30 mg of 10% Pd/C gave the desired compound. The final purification was on preparative reversed phase C18 using conditions Example 1, except that the flow rate was 18 ml/min.

C,H,N: calc: 49.27, 5.57, 8.25, found 49.15, 5.76, 8.29

$C_{31}H_{45}N_5O_7S_1$. $1.9CF_3COOH$

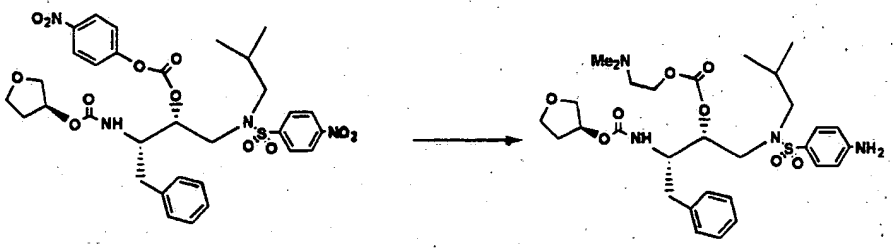
LC/MS (ES+) 632 (M+1) 1 peak at 4.71 min

Analytical HPLC(A) t=N/A min

1H:0.71 (3H,d), 0.74 (3H,d), 1.80 (2H,m), 2.03 (1H,m), 2.63 (2H,m), 2.74 (1H,m), 2.82 (3H,s), 2.92 (2H,m), 3.20 (4H,m), 3.42 (3H,m), 3.62 (2H,m), 3.75 (1H,m), 4.05 (3H,m), 4.97 (2H,m), 6.2 (1H,bs), 6.60 (2H,m), 7.22 (5H,m), 7.40 (3H,m),

13C (DMSO): 156.4, 154,0, 153.8, 138.8, 129.6, 129.5, 128.3, 126.5, 123.7, 112.7, 74.8, 72.9, 66.7, 58.2, 54.0, 53.1, 49.3, 42.3, 40.8, 36.0, 33.3, 25.8, 20.4, 20.3

Example 3



198 200

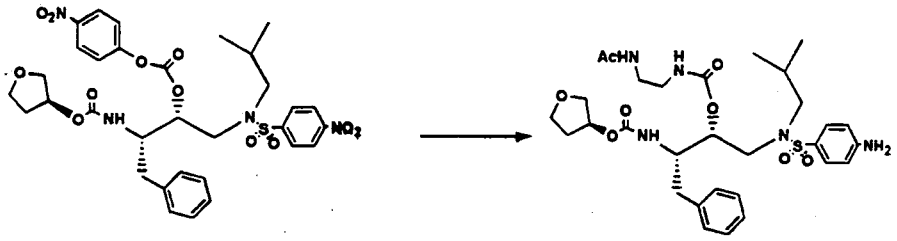
The synthesis of compound 200 from compound 198 was carried as described in Example 1, except that N,N-dimethyl-aminoethanol was used in place of di-p-nitrophenyl carbonate.

1HNMR (acetone-d6): 0.82 (6H,dd), 1.83 (2H,m), 2.07 (1H,m), 2.64 (2H,m), 2.82 (6H,s), 2.90 (2H,m), 3.19 (1H,m), 3.38 (4H,m), 3.63 (2H,m), 3.76 (1H,m), 4.17 (2YH,m), 4.40 (1H,m), 4.56 (1H,m), 4.96 (1H,m), 5.06 (1H,m), 6.06 (1H,d), 6.68 (2H,d), 7.23 (5H,m), 7.47 (2H,d).

13CNMR (acetone d6): 20.2, 20.3, 27.5, 33.4, 35.6, 43.8, 50.1, 54.2, 56.4, 58.5, 63.1, 67.4, 73.6, 76.2, 79.9, 114.2, 118.3, 127.4, 129,2, 130.1, 130.3, 139.3, 153.4, 157.0.

LC/MS: 1 peak, 621 (MH+).

Example 4



198 201

The synthesis of compound 201 from compound 198 was carried as described in Example 1, except that N-acetyl-ethylenediamine was used in place of di-p-nitrophenyl carbonate.

C,H,N: calc: 49.66, 5.64, 8.83, found 49.76, 5.98, 8.93 $C_{30}H_{43}N_5O_8S_1$. $1.4CF_3COOH$.

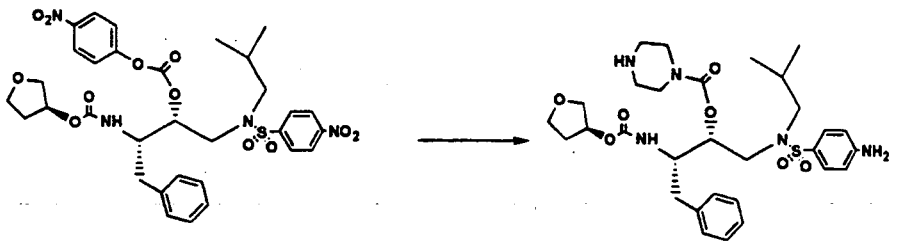
LC/MS (ES+) 634 (M+1) 1 peak at 5.08 min.

Analytical HPLC(A) t=15.92 min.

1H: d-3 acetonitrile: 0.88 (6H,dd), 1.92 (3H,s), 1.94 (2H,m), 2.17 (1H,m), 2.72 (2H,m), 2.96 (2H,m), 3.07 (3H,m), 3.29 (1H,m), 3.42 (3H,m), 3.69 (1H,m), 3.77 (1H,m), 3.82 (1H,m), 4.133 (1H,m), 4.40 (1H,bs), 5.05 (2H,m), 5.80 (1H,m), 6.10 (1H,d), 6.78 (2H,d), 6.83 (1H,bs), 7.28 (5H,m), 7.58 (2H,d).

13C (d3-acetonitrile): 157.1, 157.0, 153.2, 139.6,+130.3, +130.2, +129.2, +127.2, 126.2, +114.2, +76.0, +75.4, -73.6, -67.4, -58.2, +54.9, -50.2, -41.6, -39.8, -35.9, -33.4, +27.3, +23.1, +20.4, +20.2.

Example 5



198 202

The synthesis of compound 202 from compound 198 was carried as described in Example 1, except that mono N-Boc-piperazine was used in place of di-p-nitrophenyl carbonate.

C,H,N: calc: 48.28, 5.68, 8.41, found 48.28, 5.36, 8.28

$C_{30}H_{43}N_5O_7S_1$ x 2 CF_3COOH

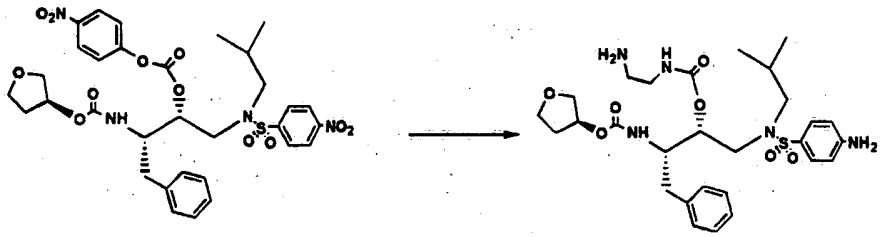
LC/MS (ES+) 618 (M+1) 1 peak at 4.36 min.

Analytical HPLC(A) t=14.84 min.

1H: d6-DMSO: 0.72 (3H,d), 0.77 (3H,d), 1.78 (2H,m), 2.09 (1H,m), 2.64 (2H,m), 2.73 (1H,m), 2.80 (1H,m), 3.08 (4H,m), 3.32 (2H,m), 3.41 (1H,m), 3.50 (4H,m), 3.54 (1H,m), 3.63 (1H,m), 3.70 (1H,m), 3.98 (1H,m), 4.89 (1H,m), 4.97 (1H,m), 6.61 (2H,d), 7.23 (5H,m), 7.42 (3H,m), 8.88 (2H,bs).

13C: (DMSO): 155.7, 153.6, 153.0, 138.4, +129.1, +129.0, +128.1, +126.1, 123.2, +112.7, +75.2, +74.4, -72.5, -66.2, -56.9, +53.1, -48.8, -42.5, -40.8, -35.0, -32.2, +26.2, +20.0, +19.8.

Example 6



198 203

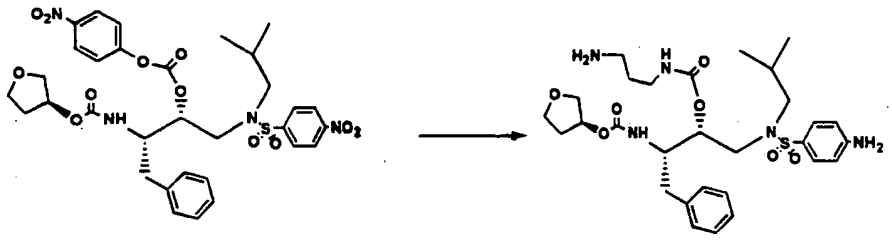
The synthesis of compound 203 from compound 198 was carried as described in Example 1, except that mono-N-Boc-ethylenediamine was used in place of di-p-nitrophenyl carbonate.

C,H,N: calc: 46.89, 5.29, 8.54, found 46.50, 5.51, 8.54

$C_{28}H_{41}N_5O_7S_1$ x 2 CF_3COOH.

LC/MS (ES+) 592 (M+1) 1 peak at 4.32 min.
Analytical HPLC(A) t=14.69 min.
1H:d-6 DMSO: 0.77 (6H,d), 1.82 (2H,m), 2.06 (1H,m), 2.57 (2H,m), 2.82 (4H,m), 2.97 (1H,m), 3.30 (5H,m), 3.55 (1H,m), 3.65 (1H,m), 3.70 (1H,m), 3.95 (1H,m), 4.88 (1H,m), 4.95 (1H,m), 6.62 (2H,d), 7.20 (6H,m), 7.39 (3H,m), 7.78 (3H,bs).
13C (dmso): 155.9, 152.9, 138.5, 129.2, 128.9, 128.1, 126.1, 122.9, 112.7, 74.7, 74.5, 72.6, 66.2, 57.2, 53.2, 49.4, 38.8, 37.94, 35.1, 32.1, 26.3, 20.0, 19.8.

Example 7

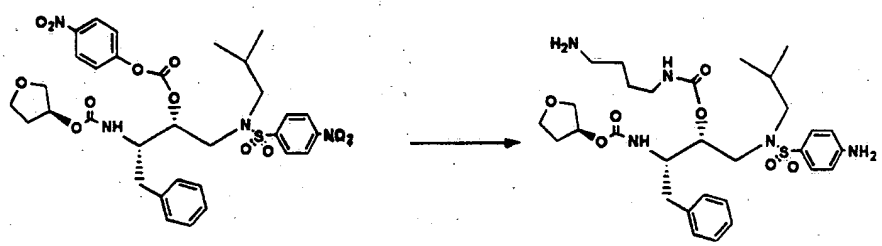


198 204

The synthesis of compound 204 from compound 198 was carried as described in Example 1, except that mono-1,3-diamino-3-N-Boc-propane was used in place of di-p-nitrophenyl carbonate.
C,H,N: calc: 49.07, 5.64, 8.89, found 48.95, 6.00, 8.92
$C_{29}H_{43}N_5O_7S_1$ x 1.6 CF_3COOH
LC/MS (ES+) 605 (M+1) 1 peak at 4.27 min.
Analytical HPLC(A) t=14.72 min.
1H:d-6 DMSO: 0.78 (6H,dd), 1.64 (2H,m), 1.83 (2H,m), 2.03 (1H,m), 2.57 (1H,m), 2.78 (4H,m), 2.94 (1H,m), 3.03 (2H,m), 3.32 (2H,m), 3.58 (1H,m), 3.63 (1H,m), 3.73 (1H,m), 3.87 (1H,m), 4.84 (1H,m), 4.92 (1H,m), 6.61 (2H,d), 7.22 (6H.m), 7.36 (1H,d), 7.28 (2H,d), 7.76 (3H,ns).

13C (dmso): 155.8, 155,7, 138.5, +129.1, +129.0, +128.0, +126.1, 122.9, +112.7, +74.6, +74.3, -72.7, -66.2, -57.2, +53.6, -49.5, -37.4, -36.7, -35.5, -32.1, -27.6, +26.2, +20.0, +19.8.

Example 8



198 205

The synthesis of compound 205 from compound 198 was carried as described in Example 1, except that 1,4-diamino-4-N-Boc-butane was used in place of di-p-nitrophenyl carbonate.

C,H,N: calc: 48.17, 5.59, 8.26, found 48.02, 5.96, 8.24

$C_{30}H_{45}N_5O_7S_1$ .2 CF_3COOH

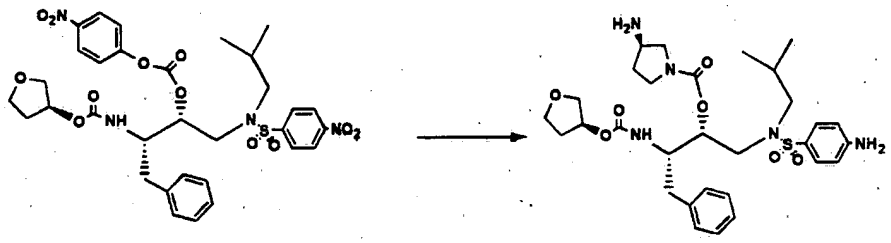
LC/MS (ES+) 620 (M+1) 1 peak at 4.36 min.

Analytical HPLC(A) t=14.93 min.

1H: d-6 DMSO: 0.77 (6H,dd), 1.43 (4H,m), 1.82 (2H,m), 2.03 (1H,m), 2.77 (4H,m), 2.95 (3H,m), 3.31 (2H,m), 3.56 (1H,m), 3.63 (1H,m), 3.70 (1H,bq), 3.82 (1H,m), 4.85 (1H,m), 4.92 (1H,m), 6.62 (2H,d), 7.2 (7H,m), 7.38 (2H,d), 7.72 (3H,bs).

13C: 155.7, 152.9, +138.6, +129.1, +129.0, +128.0, +126.1, +123.0, +112.7, +74.4, +74.3, -72.7, -66.2, -57.2, +53.7, -49.7, -38.6, -38.5, -35.4, -32.1, -26.3, +26.2, -24.4, +20.1, +19.9.

Example 9



198 206

The synthesis of compound 206 from compound 198 was carried as described in Example 1, except that (3R)-(+)-3-Boc-aminopyrrolidine was used in place of di-p-nitrophenyl carbonate.

C,H,N: calc: 48.28, 5.36, 8.28, found 47.89, 5.53, 8.57

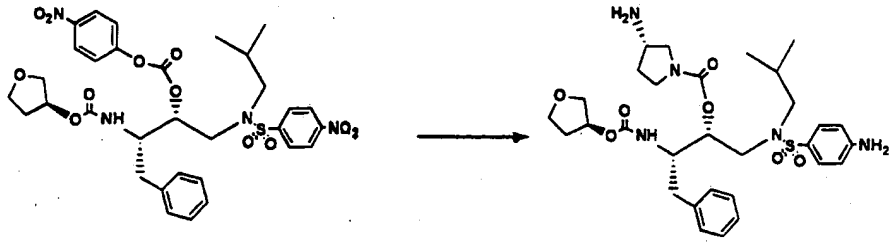
$C_{30}H_{43}N_5O_7S_1$ x 2 TFA

LC/MS (ES+) 618 (M+1) 1 peak at 4.32 min.

Analytical HPLC(A) t=14.31 min.

1H and 13C NMR: complex and overlapping mixtures of rotomers.

Example 10



198 207

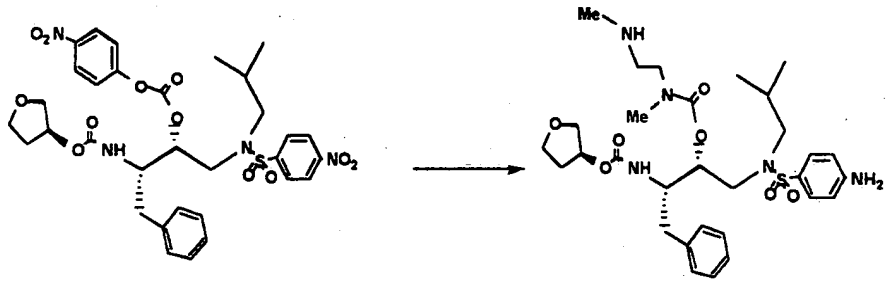
The synthesis of compound 207 from compound 198 was carried as described in Example 1, except that (3S)-(-)-3-Boc-aminopyrrolidine was used in place of di-p-nitrophenyl carbonate.

LC/MS (ES+) 618 (M+1) 1 peak at 4.19 min.

Analytical HPLC(A) t=14.75 min.

1H and 13C NMR: complex and overlapping mixtures of rotomers.

Example 11



198 308

The synthesis of compound 308 from compound 198 was carried as described in Example 1, except that N-triphenylmethyl-N,N'-dimethylethanediamine was used in place of di-p-nitrophenyl carbonate.

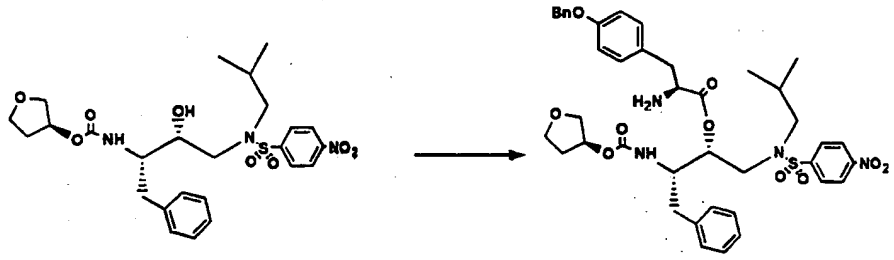
1H-NMR: 0.76 (6H,dd), 1.65 (2H,m), 1.95 (1H,m), 2.07 (1H,m), 2.7 (2H,m), 2.75 (3H,s), 2.95 (3H,m), 3.45

(2H,m), 3.7 (4H,m), 4.2 (2H,bm), 5.05 (2H,bd), 6.62 (2H,d), 7.2 (5H,m), 7.5 (2H,d).
LC/MS: 1 peak, 620 (MH+).

Example 12

General Procedures

Acylation:

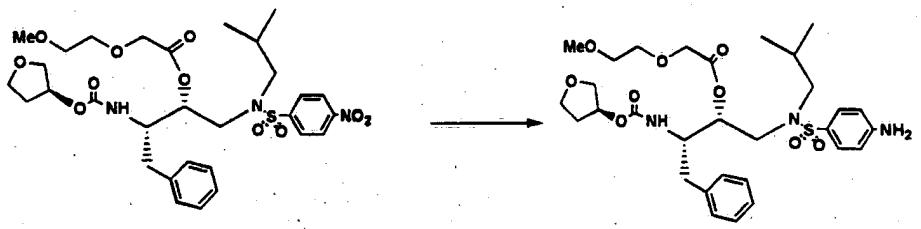


197 208

To 200mg (.37mM) of 197 dissolved in 5ml CH_2Cl_2 was added N-CBz-L-Benzyl tyrosine 183mg (.41mM) followed by 231 mg (1.12mM) DCC, followed by 29mg (.23mM) DMAP. The reaction is stirred at rt for 24hr. The precipitates present were removed by filtration. The filtrate was then concentrated in vacuo. The final compound was purified on preparative reversed phase C_{18} using purification by HPLC C_{18} Waters Delta Prep 3000 Column: YMC-Pack ODS AA 12S05-2520WT 250X20 mm I.D. S-5mm, 120Å, 0-100% B over 1/2h, flow=18 ml/min, monitored at 220 nm, B=0.1% trifluoroacetic acid in acetonitrile, A=0.1% trifluoroacetic acid in water. Analytical Column: YMC-Pack ODS AA1 2S05-2520WT 250X4.6 mmI.D. S-5mm, 120Å, 0-100% B at 1.5 ml/min. over 1/2 h, monitored at 220 nm, B=0.1% trifluoroacetic acid in acetonitrile, A=0.1% trifluoroacetic acid in water.

The aqueous phase was lyophilized to give 59 mg, (16.3%) GW431896X, (U11484-72-10) t_{HPLC}=11.71 min., MW=966.04, LC/MS=MH+967.

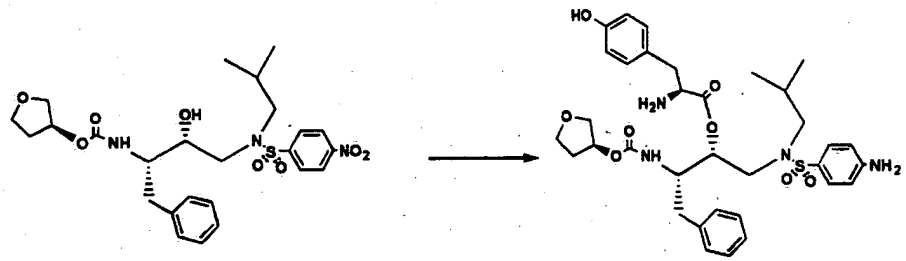
Reduction of the Nitro Functionality:



209 210

A slurry of 209 (170 mg) and 10 mg of 10% Pd.C in 95% EtOH was flushed with hydrogen in a scintillation vial equipped with septum and a stir bar. Continuous overnight hydrogenolysis under hydrogen balloon resulted in a complete conversion. The crude preparation was then filtered off the catalyst, and purified on RP C18 HPLC (Prep Nova-Pack C186 um, 60 A, gradient 0-100% B over 30 min. The desired product was collected and lyophilized affording a white fluffy solid (50 mg, 30.8%).

Example 13

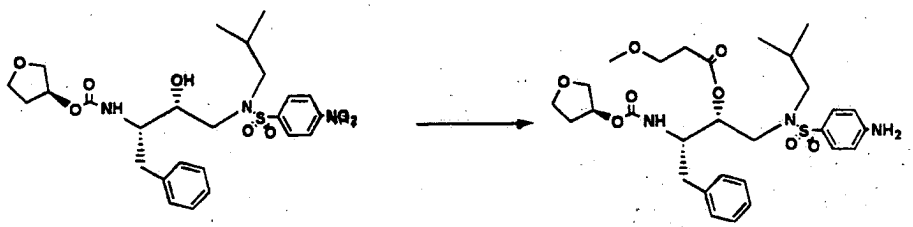


197 211

Compound 211 was obtained following the acylation and reduction procedures of Example 12. ES+ 669.2 (M+1), tHPLC=8.06 min (D), 13C NMR (DMSO) 168.9, 156.9, 155.7, 153.1, 138.1, 130.5, 129.2, 129.1, 128.1, 126.2, 124.7, 122.5, 112.8, 76.2, 74.5, 72.5, 66.1, 58.0, 53.6, 52.6, 49.2, 33.6, 32.1, 26.6, 25.3, 20.0.

tHPLC=11.71 min (D), ES+ 967 (M+1).

Example 14



197 212

212 was obtained following the procedures of Example 12.

tHPLC= 9.45 min (D), ES+ 592.2 (M+1).

13C NMR (DMSO) 171.5, 155.8, 148.9, 137.8, 129.5, 129.3, 128.5, 126.7, 115.2, 75.2, 73.8, 73.1, 68.3, 67.0, 58.7, 57.1, 53.3, 49.2, 35.4, 32.4, 26.7, 20.1, 19.8.

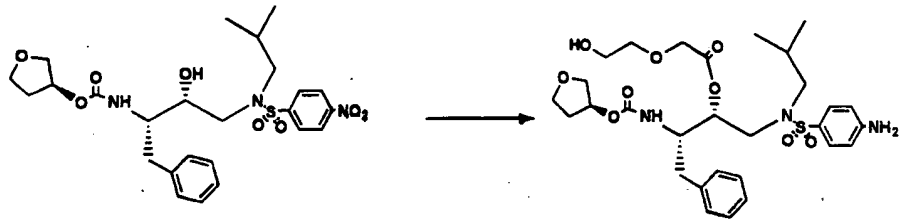
1H(CDCl3, 399.42 KHz): 8.33 (2H, d, J=8.8), 7.95 (2H, d, J=8.8), 7.23 (5H, m) 5.22 (m, 2H), 5.08 (m, 1H), 4.08 (m, 1H), 3.80-3.45 (7H, m), 3.41 (3H, s), 2.98 (m, 3H), 2.66 (m, 1H), 2.57 (m, 2H), 2.10 (s, 1H), 1.93 (2H, m), 0.82 (3H, d), 0.78 (3H, d).

ES+ 622 (M+1), 644 (M+Na)

tHPLC =10.29 min (D).

13C NMR (CDCl3): 171.3, 155.5, 149.9, 145.6, 136.9, 129.2, 128.6, 128.5, 126.8, 124.4, 76.7, 75.3, 73.2, 72.9, 68.2, 66.9, 58.7, 55.9, 53.1, 48.3, 35.3, 32.7, 26.3, 19.9, 19.8.

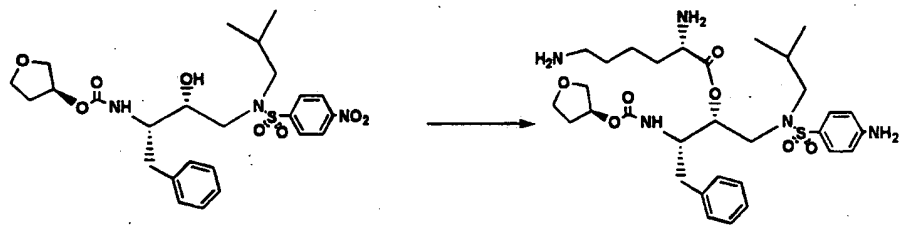
Example 15



197 213

213 was obtained following the procedure of Example 12. tHPLC = 9.21 min (D); ES+ 622 (M+1).
13C NMR (CDCl3): 170.54, 156.2, 148.6, 136.8, 129.4, 129.2, 128.6, 126.6, 115.7, 76.7, 74.6, 73.2, 71.8, 70.6, 68.2, 66.9, 58.9, 57.3, 53.8, 49.4, 36.2, 33.1, 26.8, 19.8, 19.5.
Intermediate: t HPLC = 10.05 min (D); ES+= 652 (M+H) 674 (M+Na).

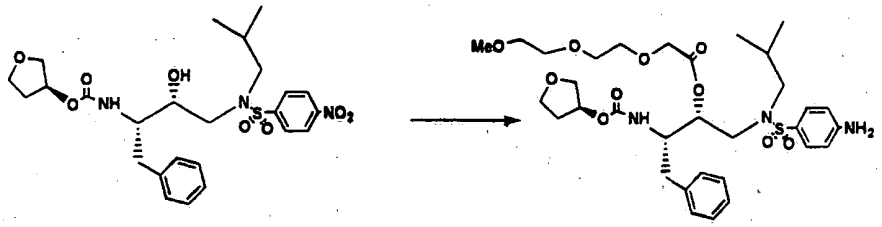
Example 16



197 214

214 was obtained following the procedure of Example 12.
ES+ 634.4 (M+1); t HPLC = 7.17 min (D).
13C (DMSO): 169.3, 155.8, 153.1, 138.0, 129.1, 129.0, 128.1, 126.3, 122.6, 112.8, 94.3, 75.6, 74.6, 72.4, 66.1, 57.8, 52.7, 52.0, 49.3, 38.4, 34.7, 32.2, 29.1, 26.6, 21.4, 20.1, 20.0.

Example 17



197 215

215 was obtained following the procedure of Example 12.

t HPLC = 9.12 min (D)

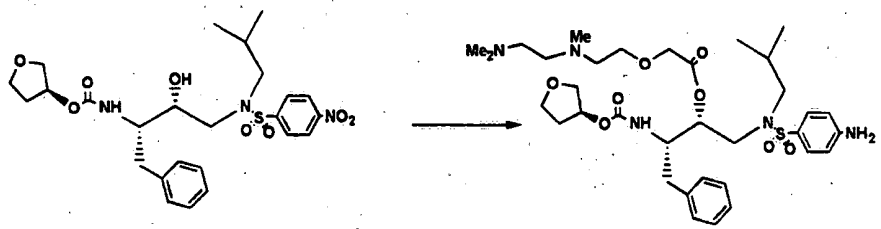
1H (DMSO) all signals broad: 7.38 (3H, br m), 7.20 (5H, br m), 6.62 (2H, br m), 5.15 (1H, br m), 4.92 (1H, br m), 4.00 (3H, m), 3.7-3.0 (16H, m), 2.78 (2H, m), 2.57 (3H, m), 2.04 (m, 1H), 1.78 (m, 2H), 0.77 (6H, m)

13C (DMSO) 170.6, 156.3, 153.7, 139.1, 129.8, 128.4, 126.7, 123.7, 113.3, 79.8, 79.2, 77.3, 76.1, 75.4, 75.2, 73.0, 71.9, 52.3, 51.8, 48.2, 46.7, 39.9, 38.7, 25.8, 22.6.

Intermediate:

t HPLC = 10.18 min (D); ES+ 696.3 (M+1).

Example 18



197 216

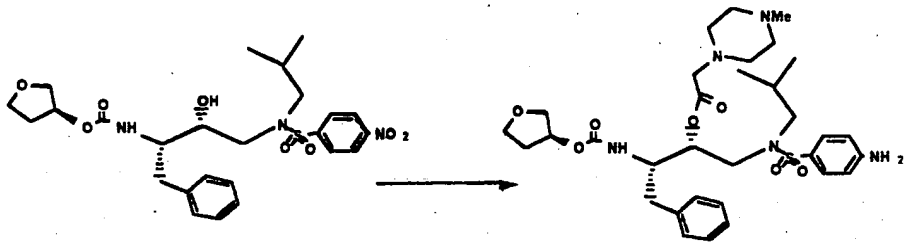
216 was obtained following the procedure of Example 12.

1H-NMR: 0.97 (6H,t), 1.95 (2H,m), 2.20 (1H,m), 2.9 (2H,m), 2.96 (6H,s), 3.00 (3H,s), 3.38 (1H,m), 3.42

(3H,m), 3.36 (1H,m), 3.6 (2H,m), 3.7 (6H,m), 3.98 (2H,m), 4.2 (2H,dd), 5,1 (1H,bs), 5.4 (1H,m), 6.8 (2H,d), 7.4 (5H,m), 7.6 (2H,d).

LC-MS: 1 peak, 692 (MH+).

Example 19



197 217

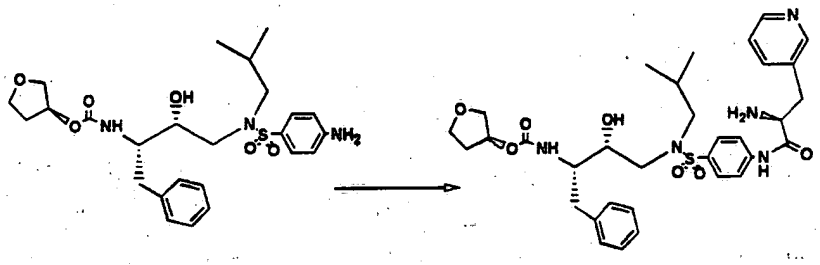
217 was obtained following the procedure of Example 12.

1H-NMR (CDCl3): 0.78 (6H,dd), 1.9 (2H,m), 2.1 (1H,m), 2.3 (3H,s), 2.9 (8H,m), 2.9 (2H,m), 3.15 (1H,m), 3.35 (1H,m), 3.5 (1H,m), 3.75 (4H,m), 4.06 (2H,s), 4.15 (2H,m), 4.9 (1H,dd), 5.05 (1H,bs), 5.2 (1H,bs), 6.63 (2H,d), 7.2 (5H,m), 7.55 (2H,d), 8.0 (2H,m).

ESMSP: 676 (MH+).

Example 20

General Procedure for N-acylated Compounds



218 219

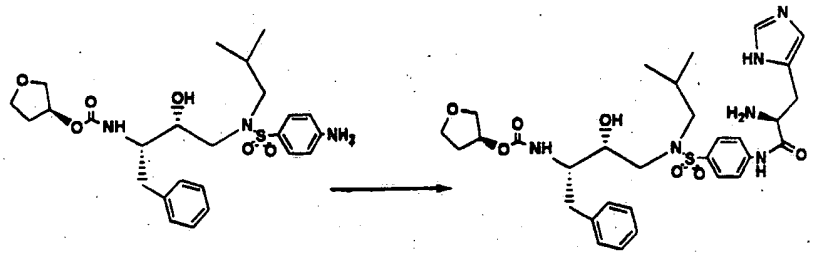
A mixture of 0.5g (1 mMol) of (3S)-Tetrahydro-3-furfuryl-N-((1S,2R)-1-benzyl-2-hydroxy-3-(N-isobutyl-4-aminobenzenesulfonamido)propyl) carbamate, 0.4g (1.5 mMol) of Boc-(S)-3-pyridyl alanine, 0.29g (1.5 mMol) EDCI and 0.1g 4-dimethylamino pyridine in 10 ml of N,N-dimethylformamide was stirred at 25° for 12 hours. The volatiles were removed in vacuo and the residue was partitioned between ethyl acetate and 1N hydrochloric acid. The organic layer was washed with 1N sodium hydroxide and brine, dried over magnesium sulfate and concentrated in vacuo. The residue was chromatographed on a 2 inch plug of silica gel (1:1 ethyl acetate: hexane) to give the desired N-acylated material.

Deprotection by treatment with 50 ml of trifluoroacetic acid, followed by co-evaporation of residual acid with methanol gave the desired prodrug as a white foam (0.2g, 26%).

H1-NMR (acetonitrile-D3): 0.95 (6H,dd), 2.0 (2H,m), 2.25 (1h,m), 2.8-3.1 (5H,m), 3.6-4.0 (7H,m), 4.25 (1H,m), 4.75 (1H,m), 5.18 (1H,m), 5.45 (1H,m), 7.0 (2H,d), 7.4 (5H,m), 7.75 (2H,d), 8.2 (1H,m), 8.8 (1H,d), 8.85 (1H,d), 9.15 (1H,s).

LC/MS: 1 peak, 654 (MH+).

Example 21



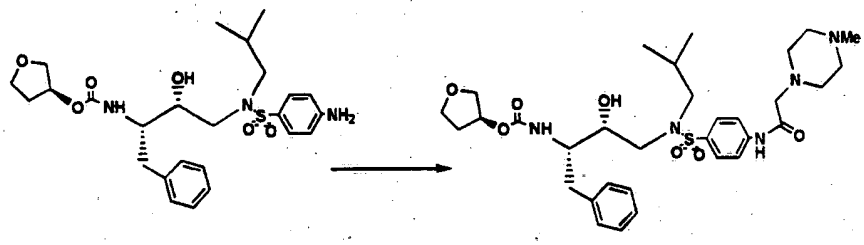
218 220

220 was obtained using the general procedure in Example 20.

1H-NMR (acetone-d6/ methanol-d4): 0.95 (6H,t), 2.0 (2H,m), 2.2 (1H,m), 2.90 (1H,dd), 2.95 (2H,d), 3.12 (1H,dd), 3.4 (2H,m), 6 (1H,d), 3.8 (5H,m), 4.4 (2H,bm), 6.82 (2H,d), 7.20 (1H,s), 7.4 (5H,m), 7.65 (2H,d), 8.0 (1H,s).

LC/MS: 1 peak, 643 (MH+).

Example 22



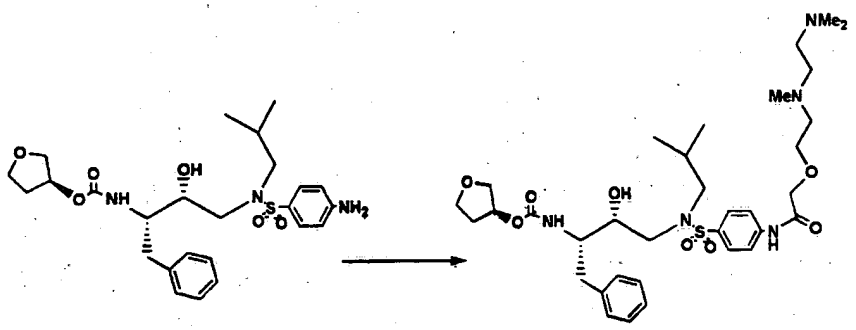
218 221

221 was obtained using the general procedure in Example 20.

1H-NMR (DMSO d-6): 0.76 (6H,t), 1.80 (2H,m), 2.10 (1H,m), 3.7 (4H,m), 3.75 (3H,s), 3.2 (5H,m), 3.58 (2H,s), 3.7 (4H,m), 4.97 (1H,bm), 5.18 (1H,bs), 6.7 (2H,d), 7.22 (5H,m), 7,45 (2H,d).

LC/MS: 1 peak, 646 (MH+).

Example 23



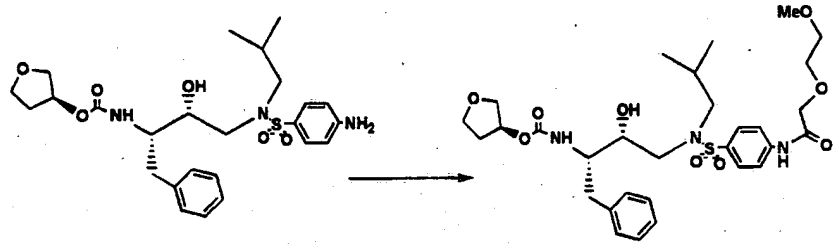
218 222

222 was obtained using the general procedure in Example 20.

1HNMR (acetonitrile d-3): 1.0 (6H,t), 2.0 (2H,m), 2.2 (1H,m), 3.00 (6H,s), 3.02 (3H,s), 3.1 (4H,m), 3.5 (3H,m), 3.8 (8H,m), 4.4 (2H,s), 5.15 (1H,bs), 7.4 (5H,m), 7.97 (2H, d), 8.04 (2H,d).

LC/MS: 1 peak, 692 (MH+).

Example 24



218 223

223 was obtained using the general procedure in Example 20.

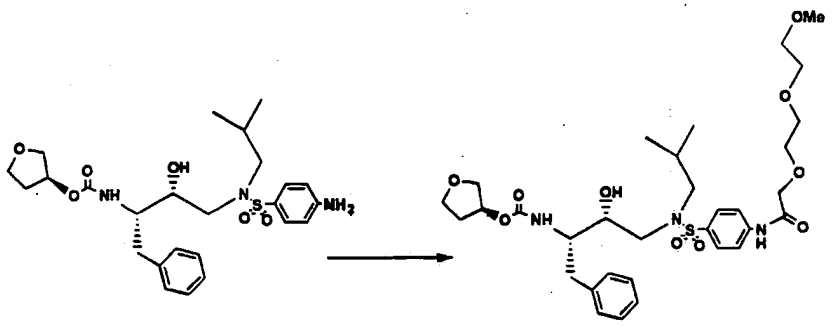
t HPLC = 9.22 min (D); ES+ 622 (M+1).

1H NMR d6-DMSO: 0.76 (6H,dd), 1.0-1.8 (15H,m), 2.03 (1H,m), 2.58 (2H,m), 2.79 (2H,m), 3.11 (1H,m), 3.28 (3H,s), 3.3-3.5 (12H,m), 3.94 (1H,m), 4.08 (1H,m), 4.94

(1H,m), 5.14 (1H,m), 6.61 (2H,d), 7.22 (5H,m), 7.40 (3H,m).

13C (DMSO) 169.7, 165.9, 152.9, 138.4, 129.2, 129.1, 128.1, 126.2, 123.1, 112.8, 74.4, 74.1, 72.5, 71.2, 69.8, 66.1, 58.1, 57.1, 52.9, 47.5, 33.4, 33.2, 26.3, 24.5, 18.9, 18.8.

Example 25



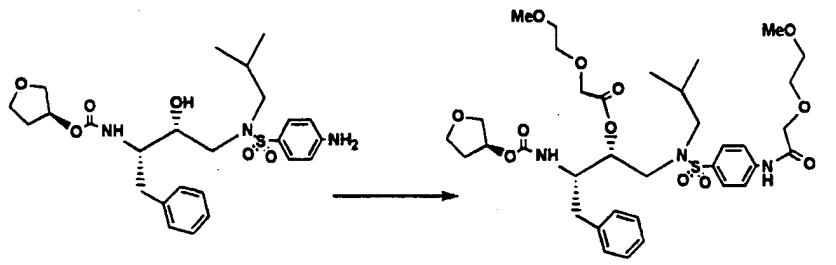
218 224

224 was obtained using the general procedure in Example 20.

Example 26

O,N-diacylated Prodrugs

The general procedure for N,O-diacylated compounds followed the protocol outlined in Example 20, above, except that a five fold excess of reagents was used relative to the starting material.



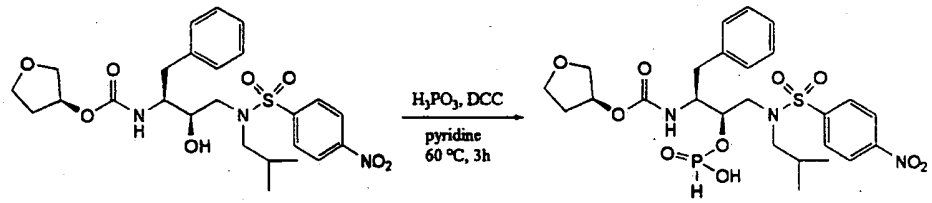
218 225

t HPLC 9.26 min (D); ES+ 738 (M+1) 760 (M+Na).

13C (DMSO): 170.2, 169.8, 156.4, 143.4, 138.8, 129.5, 128.8, 128.5, 126.8, 119.7, 74.9, 74.2, 73.7, 71.6, 70.7, 70.3, 68.0, 67.2, 59.3, 57.6, 53.8, 49.6, 35.7, 33.8, 27.1, 20.4.

1H (DMSO): 10.1 (1H, s), 7.84 (d, 2H, J=8.5), 7.76 (d, J=8.7, 2H), 7.40 (1H, d, J=9.2), 7.22 (m, 5H), 5.14 (1H, m), 4.95 (1H, m), 4.1 (m, 8H), 3.7-3.3 (m, 13H), 3.28 (s, 3H), 3.26 (s, 3H), 2.86 (m, 2H), 2.73 (m, 1H), 2.59 (m, 1H), 2.04 (m, 1H), 1.83 (m, 2H), 0.78 (m, 6H).

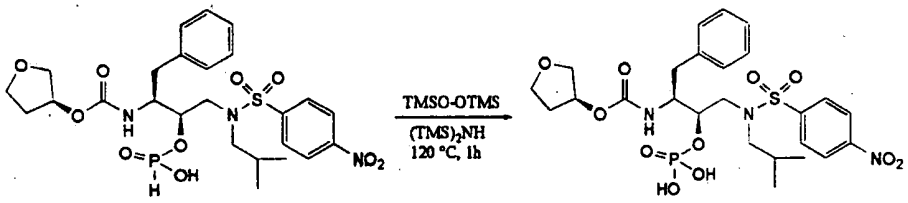
Example 27



197 226

To a mixture of 197 (2.93 g, 5.47 mmol) and phosphorous acid (Aldrich, 2.2 equiv., 12.03 mmol, 987 mg) in 20 ml pyridine was added 1,3-dicyclohexylcarbodiimide (Aldrich, 2.1 equiv., 11.49 mmol, 2.37 g) and the reaction heated to 60 °C under nitrogen for 3h. Solvent was removed *in vacuo*, the residue treated with 200 ml 0.1*N* aqueous sodium bicarbonate and stirred 1h at ambient temperature. The mixture was filtered, the filtrate acidified to pH 1.5 by addition of conc. HCl and extracted with ethyl acetate (3 x 100 ml). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo* to give 3.15g (96%) of desired product 226 which was used directly in the next reaction. HPLC: Rt = 8.91 min (96%), MS (AP+) 600.5 (M+1).

Example 28



226 227

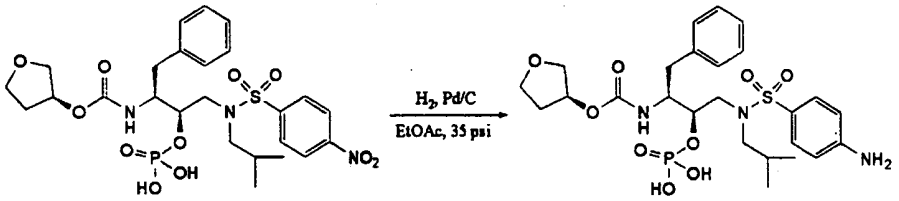
A suspension of 226 (~5.47 mmol) in 18 ml hexamethyldisilazane was stirred at 120°C until homogeneous followed by addition of bis(trimethylsilyl) peroxide (Gelest, Inc., 2.3 equiv., 12.58 mmol, 2.24 g, 2.71 ml). After 1h the mixture was cooled to ambient temperature, solvent removed *in vacuo*, the residue stirred with 100 ml methanol, solvent removed *in vacuo*, the residue stirred with 100 ml 0.1N aqueous sodium bicarbonate, acidified to pH 1.5 by addition of conc. HCl, saturated with brine and extracted with ethyl acetate (3 x 100 ml). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo* to give 2.98 g (88%) of desired product 227, which was used directly in the next reaction. HPLC: Rt = 9.28 min (90%), MS (AP+) 616.5 (M+1).

Alternatively, 227 can be synthesized directly from 197. In this method, 197 was dissolved in pyridine (300mL). The resulting solution was concentrated in vacuo to about 150 ml at 50-55°C. The solution was then cooled under N_2 to 5°C, and treated with $POCl_3$ (6.5 ml, 1.24 equiv.) over 2 minutes. The cooling bath was removed and the reaction stirred at ambient temperature for 2.5 hrs. The solution was then

cooled to 5°C and water (300 ml) was added over 30 minutes.

The resulting mixture was extracted with 4-methylpentan-2-one (MIBK, 2 x 150 ml). The combined extracts were washed with 2N HCl (2 x 250 ml). The acid washes were back extracted with MIBK (60 ml), then the combined MIBK solutions were treated with 2N HCl (150 ml). The two phase mixture was stirred rapidly and heated to 50°C for 2 hours. The reaction mixture was cooled to 20°C, the phases were separated and the MIBK solution was washed with brine (150 ml). The product, 227, was isolated by drying the solution with magnesium sulfate, filtering of the drying agent and concentrating in vacuo at 40°C to give the product as a pale yellow foam (31 g, 90% yield).

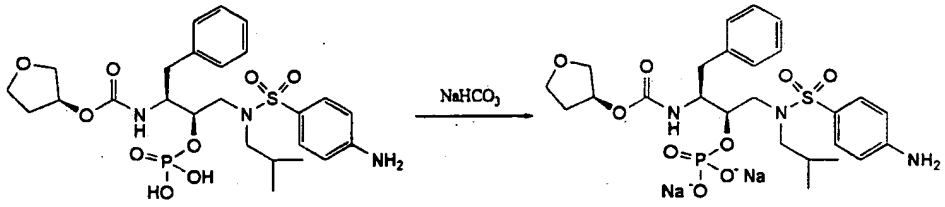
Example 29



227 228

A solution of 227 (2.98 g, 4.84 mmol) in 50 ml ethyl acetate was treated with 10% palladium on carbon (Aldrich, 300 mg) and put under 35 psi of hydrogen on a Parr shaker for 15h. Catalyst was removed by filtration and solvent removed *in vacuo* to give 2.66 g (94%) of desired product 228. HPLC: Rt = 7.23 min (92%), MS (ES+) 586.3 (M+1).

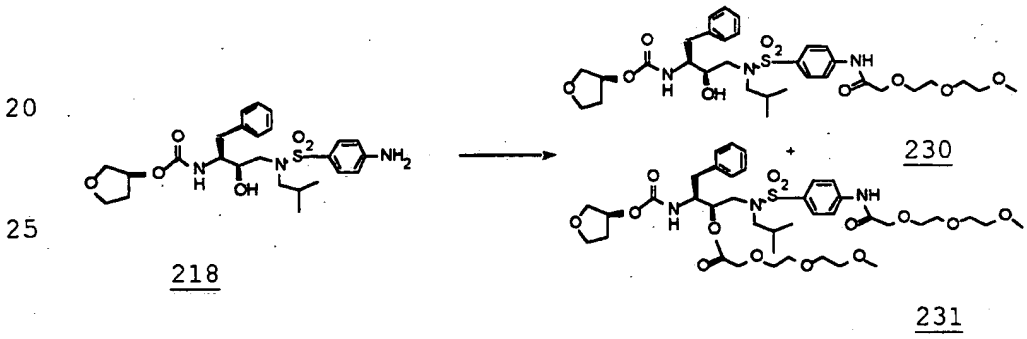
Example 30



228 229

Solid 228 (2,66 g, 4.54 mmol) was treated with 10 ml aqueous sodium bicarbonate (Baker, 3.0 equiv., 13.63 mmol, 1.14 g) and loaded onto a resin column (Mitsubishi Kasei Corp., MCI-gel, CHP-20). Distilled water was run through until the eluent was neutral followed by product elution with 1% acetonitrile in water. Pure fractions were pooled and lyophilized to give 918 mg of pure bis-sodium salt 229.

Example 31



218 231

0.53 g (3.0 mmol) 2-[2-(2-Methoxyethoxy)ethoxy] acetic acid was added to a stirred solution of 1.2 g (3.15 mmol) HATU 0.2 g (1.47 mmol) HOAt 0.4 g (4.0 mmol) NMM in 10 ml anhydrous N,N-dimethylformamide. The mixture was stirred at room temperature for 30 minutes, then 0.5 g (1 mmol) of (3S)-Tetrahydro-3-furfuryl-N-((1S,2R)-1-benzyl-2hydroxy-3-(N-isobutyl-4-aminobenzenesulfonamido)-

propyl) carbamate was added to the solution in one portion. The mixture was stirred at 20°C for an hour then at 50°C for an additional 12 hours. It was then cooled to 20°C, 50 ml of ether was added, and the solution was washed with water three times. The aqueous phase was washed with ether, and then the combined organic phases were dried with anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography to obtain the desired Mono-(N)acylated (102 mg, 15 %) and Bis-(O,N) acylated (262 mg, 32%) compounds.

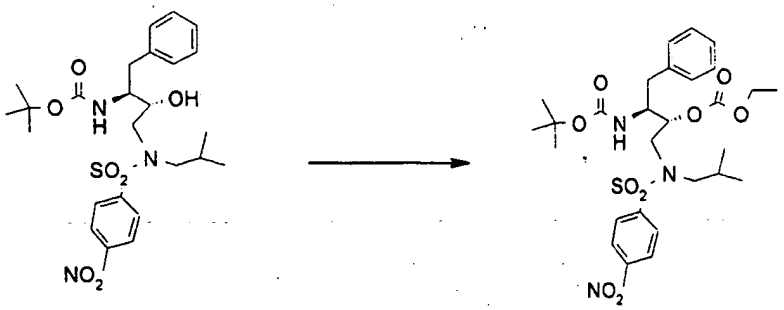
Mono-(N)-acylated: 1H-NMR(CDCl3): 0.85 (dd, 6H), 1.85 (m, 2H), 2.08 (m,1H), 2.8-3.1 (m, 7H), 3.33 (s, 3H), 3.55 (m, 3H), 3.70-3.90 (m, 8H), 4.1 (s, 2H), 5.0 (d, 1H), 5.08 (s(br), 1H), 7.2 (m, 5H), 7.70 (d, 2H), 7.80 (d, 2H), 9.09 (s, 1H).

MS(FAB+): 666 (M+1).

Bis-(O,N)-acylated: 1H-NMR(CDCl3): 0.77 (m, 6H), 1.81 (m, 1H), 1.95 (m, 1H), 2.05 (m, 1H), 2.6-3.0 (m, 6H), 3.2 (m,1H), 3.332 (s, 3H), 3.338 (s, 3H), 3.5-3.8 (m, 18H), 4.1 (s, 2H), 4.14 (s, 2H), 4.17 (m, 1H), 5.05 (m, 2H), 5.25 (s(br), 1H), 7.2 (m,5H), 7.69 (d, 2H), 7.78 (d 2H), 9.06 (s, 1H).

MS(FAB+): 826(M+1), 848(M+Na).

Example 32



1273W94 232

We dissolved 0.521g (1 mM) of 1273W94 in 5 ml THF, then cooled to -78°C under nitrogen, and added 1.56 ml (2.5 mM) of a 1.6 M solution of nBuLi in hexane. After 20 min at -78°C, we added 105 µL (1.1 mM) of ethyl chlorocarbamate and warmed up the reaction to room temperature, followed by addition of another 105 µL of ethyl chlorocarbamate.

After stirring for additional 4 hrs, the reaction was quenched with water and the organic solvent evaporated. Part of the crude product was purified on a silica gel (Rf=0.69 (1:2 ethyl acetate:hexane)), yielding 0.131g of the product.

C,H,N: calc: 46.06, 4.97, 5.88, found 45.90, 4.97, 5.88

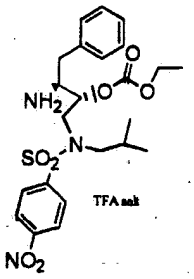
$C_{23}H_{33}N_5O_5S_1$. 2.2 TFA

LC/MS (ES+) 594 (M+1) 1 peak at 6.96 min.

Analytical HPLC(A) t=24.57 min.

13C (CDCl3): 155.8, 154.4, 149.9, 145.7, 136.8, +129.2, +128.7, +126.8, +124.2, 80.1, +76.9, -64.3, -56.2, -52.5, -48.7, -36.2, +28.1, +26.4, +20.0, +19.8, +14.3.

Example 33



233

We dissolved 0.131g of the above ethyl carbonate in 4 ml DCM, followed by 4 ml of TFA. Solvents were then removed after 45 min at room temperature, resulting in the title compound.

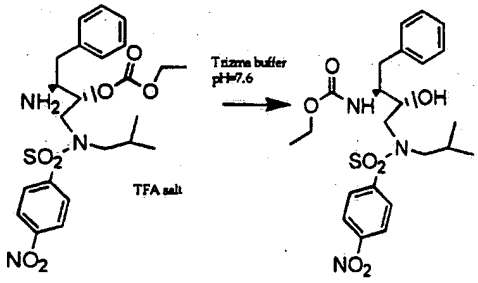
1H (DMSO): 8.37 (2H, d, J=7.2), 8.15 (2H, m), 8.00 (2H, d, J=7.0), 7.37 (5H, m), 5.04 (1H, d, J=6.9), 4.06 (2H, q, J=7.0), 3.82 ((1H, m), 3.35 (2H, m), 2.95 (4H, m), 1.82 (1H, m), 1.20 (3H, t, J=7.0), 0.72 (overlapping doublets, 6H, J=6.2).

LC/MS 1 peak at 4.76 min.

ES+ 497.3 (M+1).

Example 34

O,N-Acyloxy Rearrangement



233 234

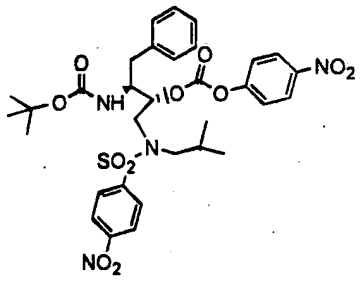
C,H,N: calc:53.26, 6.14, 7.57, found 53.22, 6.14, 7.57

$C_{23}H_{33}N_5O_5S_1$ x 0.8 TFA

LC/MS (ES+) 594 (M+1) 1 peak at 6.96 min.

Analytical HPLC(A) t=24.57 min.
1H (DMSO): 8.34 (2H, d, J=8.7), 8.02 (2H, d, J=8.0), 7.19 (5H, m), 6.98 (1H, d, J=7.2), 5.00 (1H, m), 3.83 (2H, q), 3.50 (2H, m), 3.06 (m, 2H), 2.96 (2H, m), 2.43 (1H, m), 1.97 (1H, m), 1.02 (3H, t), 0.84 (3H, d), 0.82 (3H, d). 13C (DMSO): 156.2, 150.1, 145.7, 140.0, +129.7, +129.2, +128.5, +126.3, +125.0, +71.8, -60.0, +56.2, -56.0,
-51.8, -36.0, +26.3, +20.3, +20.1, +14.6.

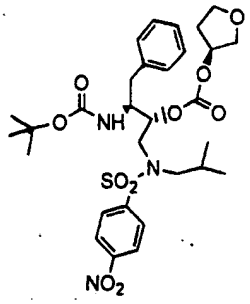
Example 35



235

Synthesis of 235 was accomplished analogous to that set forth in Example 1.
Yield 15.2%; tHPLC=25.2 min (A).
Rf=0.54 (B); ES+ 687.3 (M+1).
1H (CDCl3): 8.34 (overlapping d+d, 4H), 7.97 (d, 2H, J=8.9), 7.35 (7H, m), 5.09 (1H, m), 4.56 (1H, d, J=8.4), 4.20 (1H, m), 3.54 (1H, m), 3.00 (3H, m), 2.82 (1H, m), 1,84 (1H, m), 1.37 (9H, s), 0.84 (3H, d), 0.82 (3H, d).

Example 36



236

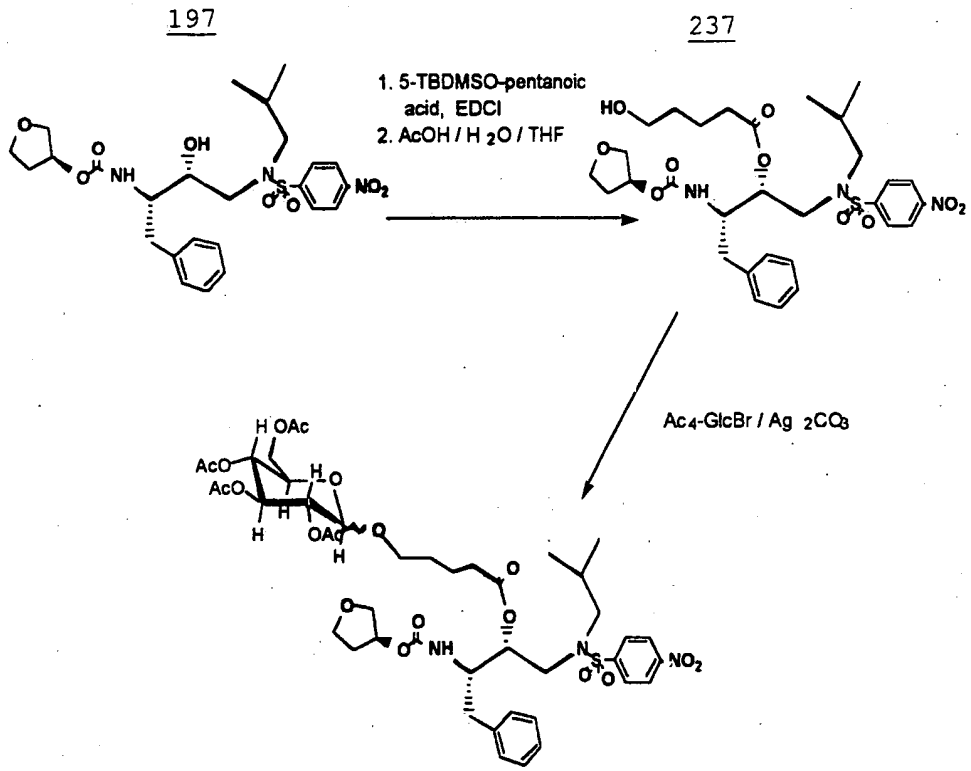
We dissolved 150 mg of 235 in 3 ml of anhydrous dioxane, added 0.35 ml of S(+)-3-OH-THF and 0.14 ml triethyl amine. The mixture was refluxed gently under nitrogen for 2 days. Conversion to 236 was quantitative. Solvents were removed and the compound purified on silica (B).

tHPLC=22.98 min (A); ES+ 636.2 (M+1).

1H NMR (CDCl3): 8.29 (2H, d), 7.91 (2H, d), 7.22 (5H, m), 5.13 (1H, m), 4.96 (1H, m), 4.52 (1H, d), 4.02 (1H, m), 3.84 (2H, m), 3.44 (1H, m), 3.36 (1H, m), 3.10 (3H, m, overlap), 2.88 (2H, m), 2.64 (1H, m), 2.14 (1H, m), 2.05 (1H, m), 1.84 (1H, m), 1.27 (9H, s), 0.78 (6H, two overl. d).

Example 37

Carbohydrate-Based Prodrugs



A mixture of 0.54g (1 mMol) of (3S)-Tetrahydro-3-furfuryl-N-((1S,2R)-1-benzyl-2-hydroxy-3-(N-isobutyl-4-aminobenzenesulfonamido)propyl) carbamate, 0.46g (2 mMol) of 5-dimethyl-tert-butyosilyloxypentanoic acid, 0.346g (1.8mMol) of EDCI and 0.556mL (4 mMol) of triethylamine in 10 ml of dimethyl formamide was stirred at rt for 24h. Another 3 mMol each of acid, EDCI and triethylamine were added and stirring was continued for an additional 96h. A third batch of acid and EDCI was added (3 mMol each) and the mixture was stirred 72h to complete the reaction. The reaction mixture was then

diluted with ethyl acetate and extracted with 1N hydrochloric acid, saturated sodium bicarbonate and water. Evaporation of the solvent and purification on silica gel (30% ethyl acetate-hexane) gave the desired product (500mg) as a waxy solid.

LCMS: 1 peak, 772.5 (M+Na)

1H NMR (CDCL3): 0.01 (6H,s), 0.78 (6H,dd), 0.95 (9H,s), 1.4-1.8 (6H,m), 1.9 (2H,m), 2.05 (1H,m), 2.3 (2H,m), 2.65 (1H,m), 2.95 (2H,m), 3.22 (1H,m), 3.4 (1H,m), 3.6 (2H,m), 3.75 (3H,m), 4,8 (1H,d), 5.1 (1H,bs), 5.2 (1H,bs), 7.2 (5H,m), 7.95 (2H,d), 8.36 (2H,d).

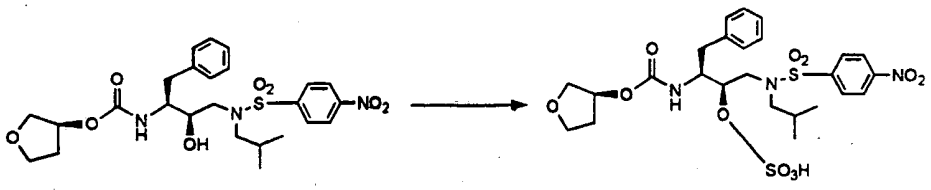
450mg of the 238 was dissolved in 30 ml of tetrahydrofuran and treated with 20 ml of water and 50 ml of acetic acid. The mixture was stirred at rt for 2h and evaporated. Titration with hexane gave the desired alcohol (290mg) as a white solid.

A mixture of 0.15g (0.24 mMol) of the alcohol produced above from the previous reaction, 0.205g (0.5 mMol) of tetraacetylglucosylbromide and 0.191g (0.7 mMol) of silver carbonate in 3 ml of dichloromethane was stirred at rt for 6h. 150mg of additional glucosyl bromide and 150 mg of silver carbonate were added and the mixture was stirred at rt overnight. The mixture was loaded onto a pad of silica gel and eluted with 30% ethylacetate-hexane to afford the desired protected carbohydrate pro-drug as a white foam (200mg).

LCMS: 1 peak, 966 (M+H).

1H-NMR (CDCl3): 0.78 (6H,dd), 1.9 (2H,m), 2.00 (3H,s), 2.02 (3H,s), 2.05 (3H,s), 2.06 (3H,s), 2.1 (2H,m), 2.3 (2H,m), 2.7 (1H,m), 2.94 (3H,bd), 3.35 (2H,m), 3.45 (2H.m), 3.8 (5H,m), 4.1 (3H,m), 4.5 (1H,d), 4.9 (1H,bs), 4.95 (1H,t,), 5.08 (4H,m), 2H,d), 8.35 (2H,d).

Example 38

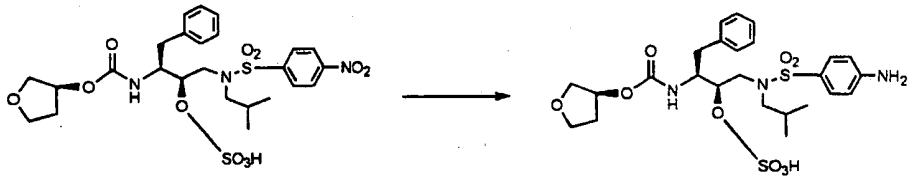


197 239

1.5 g (9.4 mmol) SO3.py complex was added to a stirred solution of 1 g (1.87 mmol) of 197 in 25 mL anhydrous tetrahydrofuran. The mixture was stirred at 20°C for 12 hours, then filtered. The filtrate was concentrated at reduced pressure, and the residue was transferred to a silica gel column and eluted with EtOAc (neat), followed by EtOAc:EtOH (4:1) to obtain 471 mg (47 %) 239 as a colorless foam.

1H-NMR(CDCl3): 0.80 (m, 6H), 1.8-2.1 (m, 3H), 4.15 (s(br), 1H), 4.8 (t, 1H), 5.04 (s (br), 1H).

MS(ES-): 614 (M-1).



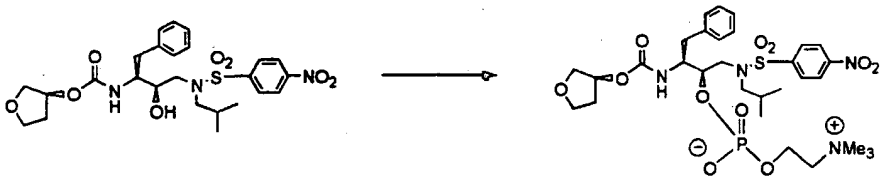
239 240

100 mg (0.162 mmol) 239 dissolved in 15 ml anhydrous tetrahydrofuran and 200 mg Pd/BaSO4 (5%) was added to the solution. The mixture was stirred under atmospheric pressure of hydrogen for 8 hours, and then the catalyst was filtered. The filtrate was concentrated under reduced pressure then dried under vacuum (~1 Hg mm, 48 hrs.) to produce 80 mg (81 %) 240 as a colorless foam.

1H-NMR(DMSO-d6): 0.85 (dd, 6H), 0.90 (m, 1H), 2.05 (m, 2H), 2.58 (m, 3H), 2.84 (dd, 1H), 3.05 (m, 2H), 3.55-

3.80 (m, 6H), 4.20 (t, 1H), 4.42 (m, 1H), 4.93 (s(br), 1H), 6.09 (s, 2H), 6.70 (d, 2H), 6.80 (d, 1H), 7.15-7.40 (m, 4H), 7.51 (d, 2H).
MS(ES-): 584 (M-1).

Example 39



197 241

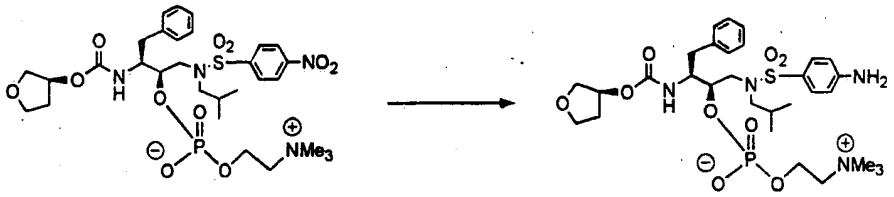
780 mg (3 mmol) 2-Chloro-1,3,2-dioxaphospholane was added to a stirred solution of 1.07 g (2 mmol) 197 and 0.7 ml (4 mmol) N,N-Diisopropylethylamine in 25 ml dichloromethane at 0°C. The mixture was allowed to warm up to room temperature and it was stirred for 2 hours. The mixture was then cooled to 0°C and 1.5 g (9.3 mmol) bromine was added in 5 ml dichloromethane. The mixture was stirred for 1 hour at 20°C, followed by evaporation under reduced pressure. An aqueous solution (50%) of 15 ml trimethylamine was added to the residue, and the mixture was stirred at 20 °C for 12 hours.

Solvents were removed under reduced pressure and 50 ml EtOAc:EtOH (9:1) was added to the residue. The solid was filtered, washed with EtOAc:EtOH (9:1) then the filtrate was concentrated under reduced pressure. The residue was chromatographed on a 3 inch plug of silica gel using ethyl acetate (neat), then methanol (neat), as eluents to obtain 1.15 g (82 %) 241 as an off-white solid.
1H-NMR(CDCl3): 0.60 (dd, 6H), 1.70 (m, 1H), 1.95 (m, 1H), 2.10 (m, 1H), 2.8-3.2 (m, 6H), 3.4 (s (br), 9H),

5.09 (s(br), 1H), 7.25 (m, 5H), 7.83 (d, 2H), 8.28 (d, 2H).

MS(ES+): 701 (M+1), 184 (phosphatidyl choline+).

Example 40



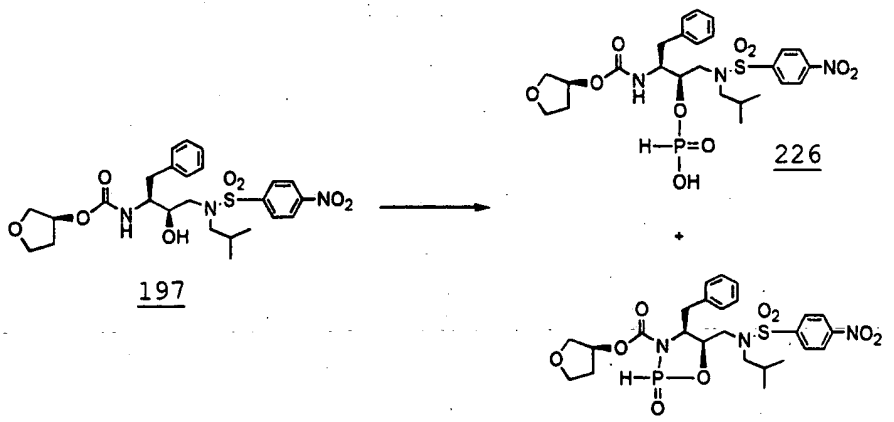
241 242

250 mg PdC (10 %) was added to a solution of 250 mg (0.35 mmol) 241 in 10 ml methanol, and the mixture was stirred under atmospheric pressure of hydrogen for 4 hours at 20°C. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was then dissolved in 10 ml water and lyophilized to obtain 174 mg (74 %) 242 as white solid.

1H-NMR(DMSO-d6): 0.82 (dd, 6H), 1.80-2.00 (m, 2H), 2.10 (m, 1H), 2.80 (m, 3H), 3.00 (m, 2H), 3.2 (s (br), 9H), 4.0-4.3 (m, 4H), 4.91 (s(br), 1H), 6.08 (s(br), 2H), 6.67(d, 2H), 7.30 (m, 5H), 7.48 (d, 2H), 8.12 (d, 1H).

MS(ES+): 671 (M+1), 184 (phosphatidyl choline+).

Example 41



197 226

243

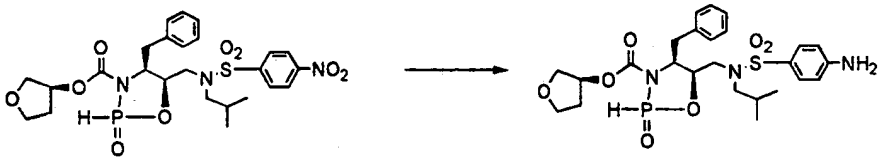
0.175 ml (2 mmol) phosphorus trichloride was added to a stirred solution of 1.07 g (2 mmol) 197 and 0.35 ml (2 mmol) N,N-Diisopropylethylamine in 25 ml dichloromethane at 20°C. The mixture was stirred for 4 hours at 20°C, then 1 ml water was added and stirred for an additional 12 hours at 20°C. 3 g anhydrous magnesium sulfate was added to the mixture and it was stirred for 30 minutes, then filtered. The filtrate was concentrated under reduced pressure and purified by silica gel chromatography using EtOAc:Hexane (4:1), then EtOAc:EtOH (1:1), to obtain 402 mg (48%) 226 and 427 mg (36%) 243.

226:

1H-NMR(DMSO-d6): 0.82 (dd, 6H), 1.84 (m, 1H), 1.98 (m, 1H), 2.10 (m, 1H), 2.68 (dd, 1H), 2.9-3.2 (m, 4H), 3.6-3.8 (m, 3H), 3.94 (t, 1H), 4.30, (s(br), 1H), 4.97 (s(br), 1H), 7.30 (m, 5H), 8.14 (d, 2H), 8.43 (d, 2H).
MS(ES-): 598 (M-1).

243: (1:1 mix of diastereomers):
1H-NMR(CDCl3): 0.80 (m, 6H), 1.8-2.1 (m, 4H), 2.8-3.2 (m, 6H), 3.7-3.9 (m, 4H), 4.15 (m, 1H), 4.8-5.15 (m, 2H), 5.57, 5.72 ((d,d), 1H), 7.25 (m, 5H), 7.95 (dd, 2H), 8.35 (m, 2H).
MS(ES-): 580 (M-1), 598 ((M+H2O)-1).

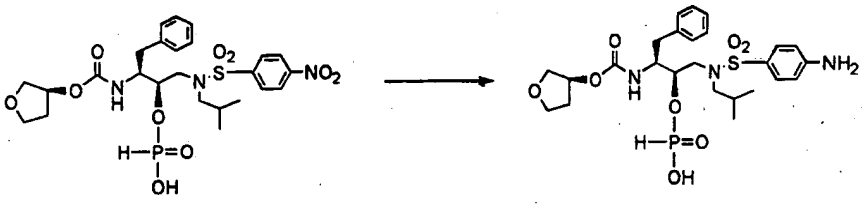
Example 42



243 244

The reduction was carried out as described in Example 40; (Yield: 79%).
1H-NMR(DMSO-d6): 0.81 (dd, 6H), 1.82 (m, 1H), 1.95 (m, 1H), 2.08 (m, 1H), 2.6-3.15 (m, 6H), 3.6-3.75 (m, 3H), 4.03 (t, 1H), 4.28, (m, 1H), 4.96 (s(br), 1H), 6.07 (s, 2H), 6.65 (d, 2H), 7.25 (m, 5H), 7.42 (d, 2H).
MS(ES-): 568 (M-1).

Example 43



226 245

The reduction was carried out as described in Example 40; (Yield: 98 %).
(1:1 mix of diastereomers):
1H-NMR(DMSO-d6): 0.82 (m, 6H), 1.75-2.0 (m, 2H), 2.05 (m, 1H), 2.6-3.2 (m, 6H), 3.55-3.8 (m, 4H), 4.02, 4.22 (m, t, 1H), 4.75 (m, 1H), 4.90, 5.01 ((d,d), 1H), 6.12 (s, 1H), 6.68 (d, 2H), 7.30 (m, 5H), 7.49 (d, 2H).
MS(ES-): 550 (M-1), 568 ((M+H2O)-1).

Example 44

Pharmacokinetics In Sprague-Dawley Rats Following Single Oral Dose

In order to study the pharmacokinetics of the prodrugs of this invention, we administered single oral doses of a series of prodrugs of this invention, as well as VX-478, to male and female Sprague-Dawley rats. Administration of molar equivalents of a series of

prodrugs of this invention in a variety of pharmaceutical vehicles was tested.

Separate groups of male and female Sprague-Dawley rats (3/sex/group) received oral doses of compound 229 by oral gavage, in different vehicles at the same dose equivalent (40 mg/kg molar equivalent of VX-478). The different vehicles for compound 229 were: 1) water; 2) 5/4/1; 3) PEG 400; 4) TPGS/PEG 400; and 5) PEG. The vehicles for VX-478 were: 1) 33% TPGS/PEG400/PEG; and 2) 12.5 % TPGS/PEG 400/PEG.

Blood samples were collected following administration at various time intervals and analyzed for the presence of both compound 229 and its metabolite, VX-478, by HPLC and MS methods. The results of this study are tabulated below (Table IV).

TABLE IV

Compound	229	229	229	229	VX-478	VX-478
vehicle	H_2O	H_2O:PG:EtOH 5:4:1	PEG 400	TPGS/PEG 400/PG	33% TPGS/ PEG 400/ PG	12.5% TPGS/ PEG 400/PG
number of rats	3	3	3	3	6	≥3
Molar equiv. dose/ 478 Dose (mg/Kg)	40 PO	40 PO	40 PO	40 PO	41 PO	50 PO
AUC (ug*hr/ml)	11.7± 4.8	10.6 ± 7.4	7.4 ± 1.8	8.2 ± 1.6	29.6 ± 5.8	16.2 ± 1.8
Cmax (μM)	7.1± 1.7	3.3 ± 0.6	3.1 ± 0.3	3.0 ± 0.7	14.0 ± 2.2	6.0 ± 1.0
half life (hr)	1.7*	3.4*	2.8*	2.8*	2.5 ± 0.9	2.2 ± 1.0
Relative Avail. of VX-478	39.5† 90.2††	35.8† 81.8††	25.0† 57.1††	27.7† 63.3††	reference	reference

- a dose of 50 mg / Kg of compound 229 is equal to 40 mg/ Kg of VX-478.
- no compound 229 was detected in plasma at 15 min. (first data point).

* Represents the harmonic mean

† Relative availability of VX-478 when compared to a prototype clinical formulation

†† Relative availability of VX-478 when compared to a prototype toxicology formulation

We performed a similar study on dogs using both a solid capsule formulation of compound 229 and an ethanolic/methyl cellulose solution formulation, as compared to a TPGS-containing solution formulation of VX-478. The results from this study are presented below in Table V.

TABLE V

Compound	229	229	VX-478
vehicle	solid capsule	methyl cellulose in 5% EtOH/water	22% TPGS/PEG 400/PG
number of dogs	2	2	>2
Molar equiv. dose/ 478 Dose (mg/Kg)	17 PO	17 PO	17 PO
AUC (ug*hr/ml)	16.7 ± 2.7	14.2 ± 3.2	23.5 ± 7.4
Cmax (µg/ml)	6.1 ± 1.7	6.3 ± 0.3	6.8 ± 1.1
Tmax (hr)	2.3 ± 0.6	0.5 ± 0.5	1.0 ± 0.8
Relative Avail. of VX-478 (%)	71.1	60.4	reference

The results demonstrate that oral administration of compound 229 as an aqueous solution resulted in improved bioavailability in comparison to the other vehicles studied. Also, following administration of compound 229, none of that compound was detected in the first time point blood sample (or later samples), suggesting first pass metabolism to VX-478. Comparison of the aqueous dose of compound 229

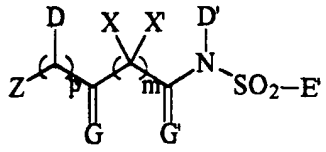
with the two non-aqueous formulations used for VX-478 indicated equivalence in delivery as illustrated by the range found for the bioavailability.

While we have described a number of embodiments of this invention, it is apparent that our basic constructions may be altered to provide other embodiments which utilize the products and processes of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims, rather than by the specific embodiments which have been presented by way of example.

CLAIMS

We claim:

1. A compound of formula I:



(I)

wherein:

each Z is selected from the group consisting of $-N(D)SO_2E$; $-N(H)A$; $-N(D)A$; $-N(H)E$; $-N(H)C(O)N(D)(E)$; $-N(H)-Ht$; $-Ht$ and $-N(D)-Ht$;

each A is independently selected from the group consisting of H; Ht; $-R^1-Ht$; $-R^1-C_1-C_6$ alkyl, which may be optionally substituted with one or more groups selected from the group consisting of hydroxy, C_1-C_4 alkoxy, Ht, $-O-Ht$, $-NR^2-CO-N(R^2)(R^2)$, $-NR^2-CO-OR^2$ and $-CO-N(R^2)(R^2)$; and $-R^1-C_2-C_6$ alkenyl, which may be optionally substituted with one or more groups selected from the group consisting of hydroxy, C_1-C_4 alkoxy, Ht, $-O-Ht$, $-NR^2-CO-N(R^2)(R^2)$, $-CO-N(R^2)(R^2)$ or R^{10};

each Ht is independently selected from the group consisting of C_3-C_7 cycloalkyl; C_5-C_7 cycloalkenyl; C_6-C_{10} aryl; phenyl fused with heterocycle; and heterocycle; wherein any member of said Ht may be optionally substituted with one or more substituents selected from the group consisting of oxo, $-OR^2$, $-R^2$, $-N(R^2)(R^2)$, $-NHOH$, $-R^2-OH$, $-CN$, $-CO_2R^2$, $-C(O)-N(R^2)(R^2)$, $-S(O)_2-N(R^2)(R^2)$, $-N(R^2)-C(O)-R^2$, $-C(O)-R^2$, $-S(O)_n-R^2$, $-OCF_3$, $-S(O)_n-D$, $-N(R^2)-S(O)_2(R^2)$, halo, $-CF_3$, $-NO_2$, $-R^6$, $-O-R^6$, $-C(O)N(D)(D)$ and $-C(O)N(H)D$, $-OR^{10}$, $-SR^{10}$, $-R^{10}$, $-N(R^2)(R^{10})$ or $-N(R^{10})_2$;

each D and D' is independently selected from the group consisting of R^6; $-N(R^2)(R^2)$; C_1-C_6 alkyl, which may be optionally substituted with one or more groups selected from C_3-C_6 cycloalkyl, $-OR^2$, $-R^3$, $-O-R^6$ $-S-R^6$ and R^6; C_2-C_4 alkenyl, which may be optionally substituted with one or more groups selected from the group consisting of C_3-C_6 cycloalkyl, $-OR^2$, $-R^3$, $-O-R^6$ and R^6; C_3-C_6 cycloalkyl, which may be optionally substituted with or fused with R^6; and C_5-C_6 cycloalkenyl, which may be optionally substituted with or fused with R^6;

each E and E' is independently selected from the group consisting of Ht; -O-Ht; Ht-Ht; $-O-R^3$; $-NR^2R^3$; C_1-C_6 alkyl, which may be optionally substituted with one or more groups selected from the group consisting of R^{10}, R^4 and Ht; and C_2-C_6 alkenyl, which may be optionally substituted with one or more groups selected from the group consisting of R^{10}, R^4 and Ht;

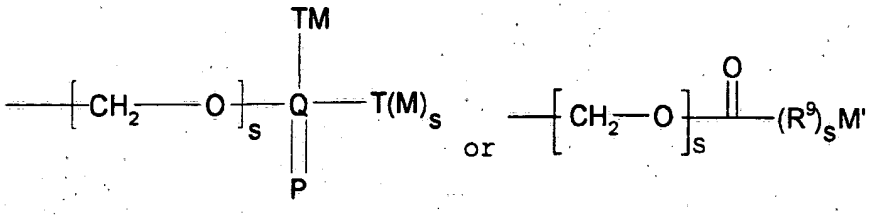
each R^1 is independently selected from the group consisting of $-C(O)-$, $-S(O)_2-$, $-C(O)-C(O)-$, $-O-C(O)-$, $-O-S(O)_2$, $-NR^2-S(O)_2-$, $-NR^2-C(O)-$ and $-NR^2-C(O)-C(O)-$;

each R^2 is independently selected from the group consisting of H, $-R^6$, and C_1-C_4 alkyl optionally substituted with R^6;

each R^3 is independently selected from the group consisting of H, Ht, C_1-C_6 alkyl and C_2-C_6 alkenyl wherein any member of said R^3, except H, may be optionally substituted with one or more substituents selected from the group consisting of $-OR^2$, $-C(O)-NH-R^2$, $-S(O)_n-N(R^2)(R^2)$, Ht, -CN, $-SR^2$, $-CO_2R^2$, $NR^2-C(O)-R^2$;

each R^4 is independently selected from the group consisting of $-OR^2$, $-C(O)-NHR^2$, $-S(O)_2-NHR^2$, halo, $-NR^2-C(O)-R^2$, -CN, $-N(R^2)(R^2)$, $-NO_2$, $-C(O)N(D)(D)$ and $-C(O)N(H)D$;

each R^{10} is independently selected from



;

wherein each M is independently selected from H, Li, Na, K, Mg, Ca, Ba, $-N(R^2)_4$, C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl, or $-R^6$; wherein 1 to 4 $-CH_2$ radicals of the alkyl or alkenyl group, other than the $-CH_2$ that is bound to T, is optionally replaced by a heteroatom group selected from O, S, S(O), $S(O_2)$, or $N(R^2)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, $-OR^2$, $-R^2$, $N(R^2)_2$, $N(R^2)_3$, R^2OH, -CN, $-CO_2R^2$, $-C(O)-N(R^2)_2$, $S(O)_2-N(R^2)_2$, $N(R^2)-C(O)-R_2$, $C(O)R^2$, $-S(O)_n-R^2$, OCF_3, $-S(O)_n-R^6$, $N(R^2)-S(O)_2(R^2)$, halo, $-CF_3$, or $-NO_2$;

M' is H, C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl, or $-R^6$; wherein 1 to 4 $-CH_2$ radicals of the alkyl or alkenyl group is optionally replaced by a heteroatom group selected from O, S, S(O), $S(O_2)$, or $N(R^2)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, $-OR^2$, $-R^2$, $-N(R^2)_2$, $N(R^2)_3$, $-R^2OH$, -CN, $-CO_2R^2$, $-C(O)-N(R^2)_2$, $-S(O)_2-N(R^2)_2$, $-N(R^2)-C(O)-R_2$, $-C(O)R^2$, $-S(O)_n-R^2$, $-OCF_3$, $-S(O)_n-R^6$, $-N(R^2)-S(O)_2(R^2)$, halo, $-CF_3$, or $-NO_2$;

T is O, S, $N(R^2)_2$, or, when M is absent, H;

Q is P or S;

P is O or S; and

each s is independently 0 or 1;

R^9 is $C(R^2)_2$, O or $N(R^2)$; and wherein when Q is S, T is not S; and

each R^6 is independently selected from the group consisting of aryl, carbocycle and heterocycle, wherein said carbocycle or heterocycle may be optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^5$, $-R^5$, $-N(R^5)(R^5)$, $-N(R^5)-C(O)-R^5$, $-R^5-OH$, $-CN$, $-CO_2R^5$, $-C(O)-N(R^5)(R^5)$, halo and $-CF_3$;

each R^5 is independently selected from the group consisting of H and C_1-C_3 alkyl;

each n is independently 1 or 2;

m is an integer selected from 1, 2 and 3;

p is an integer selected from 0 and 1;

each G and G' is independently selected from the group consisting of H_2 and O;

each X and X' is independently selected from the group consisting of hydrogen; -OH; $-NH_2$; -SH; D; $-OR^{10}$, halogen and, if X and X' are taken together, oxygen;

provided that at least one X or X' is $-OR^{10}$ and the other geminal X' or X is H; and

each Y is independently selected from the group consisting of hydrogen and D.

2. The compound according to claim 1 wherein G and G' are oxygen, and the X and X' on the carbon adjacent to the carbonyl are independently selected from the group consisting of H, OH, F, or taken together, oxygen.

3. The compound according to claim 1 wherein G and G' are oxygen and m is 1.

4. The compound according to claim 1 wherein G' is H_2, p is zero, and m is 1.

5. The compound according to claim 1 wherein G' is H_2, p is zero, and m is 2.

6. The compound according to claim 5 wherein G is H_2.

7. The compound according to claim 6 wherein Z is -N(D)A.

8. The compound according to claim 1 wherein G' is H_2, p is zero, m is 3, and one of X and X' is $-OR^{10}$ and the other of X and X', if present, is H;

9. The compound according to any of claims 3-6 wherein:

each D and D' is independently selected from the group consisting of C_1-C_6 alkyl, which may be optionally substituted with R^6;

each E and E' is independently selected from C_5-C_6 aryl, which may be optionally substituted with R^4;

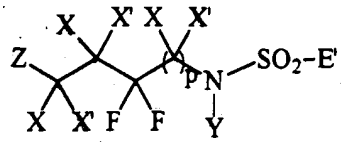
each R^4 is independently selected from the group consisting of $-OR^2$, $-N(R^2)(R^2)$ and $-NO_2$;

each Z is independently selected from the group consisting of -N(H)Ht; -N(H)A; -N(D)A and -Ht;

each Ht is independently selected from the group consisting of C_6-C_{10} aryl and 5-10 membered saturated or unsaturated heterocycle, wherein any member of said Ht may be optionally substituted with one or more substituents, the same or different, selected from the group consisting of $-OR^2$, R^2, $-N(R^2)(R^2)$, $-NO_2$, $-C(O)N(R^2)(R^2)$ and $-S(O)_n-R^6$, $-OR^{10}$, $-SR^{10}$, $-R^{10}$, $-N(R^2)(R^{10})$ or $-N(R^{10})_2$; and

each A is independently selected from the group consisting of H; $-R^1$-Ht and $-R^1$-C_1-C_6 alkyl.

10. A compound of formula II:



(II)

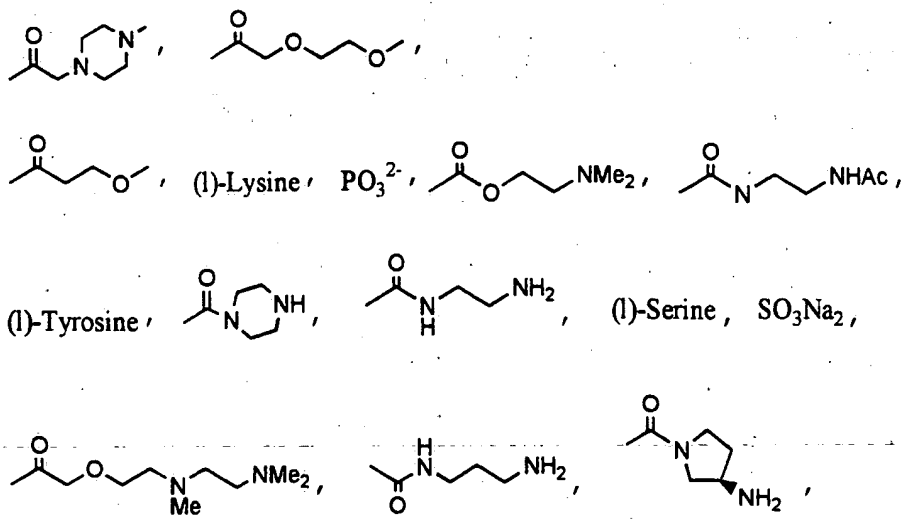
wherein:

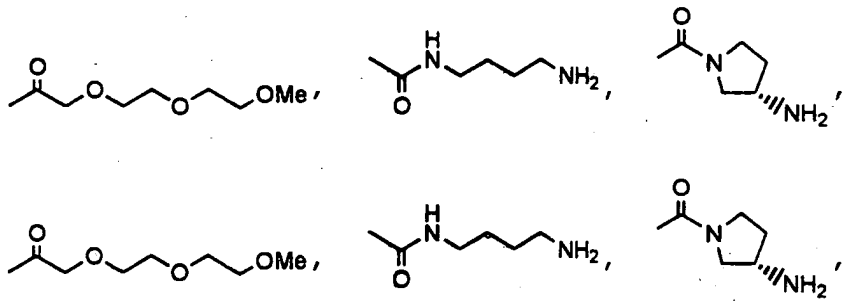
each Z, A, Ht, D, D', E, E', R^1, R^2, R^3, R^4, R^5, R^6, R^9, R^{10}, M, M', T, Q, P, s, n, m, p, G, G', X, X', and Y is as defined in claim 1.

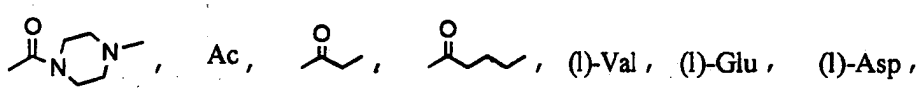
11. The compound according to any of claims 1-8 and 10 wherein E' is -Ht or $-R^2$-Ht.

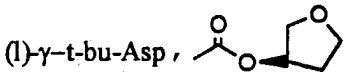
12. The compound according to claim 11 wherein E' is phenyl-R^7.

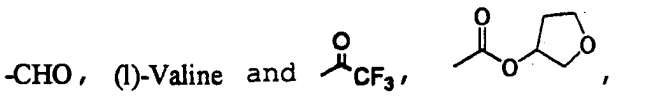
13. The compound according to any of claims 1-8 and 10-12 wherein R^{10} is selected from the group consisting of:

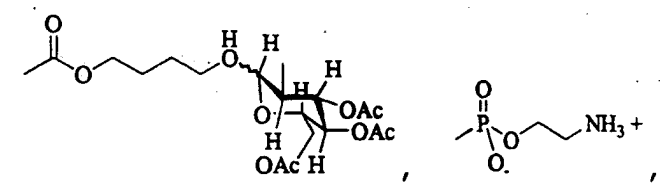


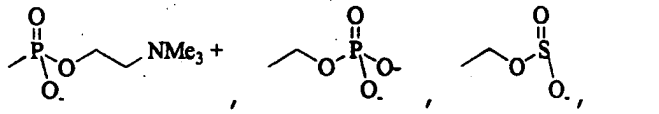












PO_3K_2, PO_3Ca, PO_3-spermine, PO_3-(spermidine)$_2$ or PO_3-(meglamine)$_2$.

14. A pharmaceutical composition, comprising a compound according to any one of claims 1 to 13 in an amount effective to treat infection by a virus that is characterized by an aspartyl protease; and a

pharmaceutically acceptable carrier, adjuvant or vehicle.

15. The pharmaceutical composition according to claim 14, wherein said virus is HIV.

16. The pharmaceutical composition according to claim 14, wherein said pharmaceutical composition is formulated for oral administration.

17. The pharmaceutical composition according to claim 14, further comprising one or more agents selected from an anti-viral agent, an HIV protease inhibitor other than a compound according to either of claims 1 or 10, and an immunostimulator.

18. The pharmaceutical composition according to claim 17, further comprising one or more agents selected from zidovudine (AZT), zalcitabine (ddC), didanosine (ddI), stavudine (d4T), 3TC, 935U83, 1592U89, 524W91, saquinavir (Ro 31-8959), L-735,524, SC-52151, ABT 538 (A80538), AG 1341, XM 412, XM 450, CPG 53,437, or tuscarasol.

19. A method for inhibiting aspartyl protease activity in a mammal, comprising the step of contacting administering to said mammal a pharmaceutical composition according to claim 14.

20. A method for treating HIV infection in a mammal comprising the step of administering to said mammal a pharmaceutical composition according to any one of claim 14.

21. The method according to claim 20, wherein said mammal is additionally administered one or more additional agents selected from an anti-viral agent, an HIV protease inhibitor other than a compound according to either of claims 1 or 10, and an immunostimulator either as a part of a single dosage form with said pharmaceutical composition or as a separate dosage form.

22. The method according to claim 21, wherein said additional agent is selected from zidovudine (AZT), zalcitabine (ddC), didanosine (ddI), stavudine (d4T), 3TC, 935U83, 1592U89, 524W91, saquinavir (Ro 31-8959), L-735,524, SC-52151, ABT 538 (A80538), AG 1341, XM 412, XM 450, CPG 53,437, or tuscarasol.

23. The method according to claim 20, wherein said step of administering comprises oral administration.